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Dated 10 January 2002

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1/77

Request for grant of a patent

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THE PATENT OFFICE
08 JUN 2001
LONDON

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference PA495A

11JUN01 E635860-1 C72481
P01/7700 0.00-0114000.3

2. Patent application number *(The Patent Office will fill in this part)* **0114000.3** 08 JUN 2001

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CALTECH R & D LIMITED
208 BATH ROAD
SLOUGH
SL1 3WE

Patents ADP number *(if you know it)* 8121485001

If the applicant is a corporate body, give the country/state of its incorporation UK

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)*

Victoria McKinney
PATENT DEPT.
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"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)* 8162893001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
—	—	—

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
—	—

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
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YES

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Priority documents	0
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application.

FOR AND ON BEHALF OF CELLTECH R & D LIMITED

Signature — Date: 8th June 2001

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr S THORN 01753 447928

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CHEMICAL COMPOUNDS

This invention relates to a series of phenylalanine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T. A., Nature, 346, 425, (1990); Springer, T. A., Cell, 76, 301, (1994)]. Specific cell surface molecules collectively referred to as cell adhesion molecules mediate many of these interactions.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 16 different integrin alpha chains and 8 different integrin beta chains have been identified [Newman, P. *et al*, Molecular Medicine Today, 304, (1996)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in the field. Thus the integrin $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA-4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised to date [Sonnenberg, A., Current Topics in Microbiology and Immunology, 184, 7, (1993)].

The importance of integrin function in normal physiological responses is highlighted by two human deficiency diseases in which integrin function is defective. Thus in the disease termed Leukocyte Adhesion Deficiency (LAD) there is a defect in one of the families of integrins expressed on

leukocytes [Marlin, S. D. *et al*, J. Exp. Med. 164, 855, (1986)]. Patients suffering from this disease have a reduced ability to recruit leukocytes to inflammatory sites and suffer recurrent infections, which in extreme cases may be fatal. In the case of patients suffering from the disease termed Glanzman's thrombasthenia (a defect in a member of the beta 3 integrin family) there is a defect in blood clotting (Hodivala-Dilke, K. M., J. Clin. Invest. 103, 229, (1999)].

The potential to modify integrin function in such a way as to beneficially modulate cell adhesion has been extensively investigated in animal models using specific antibodies and peptides that block various functions of these molecules [e.g. Issekutz, T. B., J. Immunol. 149, 3394, (1992); Li, Z. *et al*, Am. J. Physiol. 263, L723, (1992); Mitjans, F. *et al*, J. Cell Sci. 108, 2825, (1995); Brooks, P. C. *et al*, J. Clin. Invest. 96, 1815, (1995); Binns, R. M. *et al,* J. Immunol. 157, 4094, (1996); Hammes, H.-P. *et al*, Nature Medicine 2, 529, (1996); Srivata, S. *et al* , Cardiovascular Res. 36, 408 (1997)]. In particular an anti $\alpha_4\beta_7$-antibody has demonstrated both clinical and histologic improvement of inflammatory activity and disease in a non-human primate model of inflammatory bowel disease [Hesterberg, P.E. *et al*, Gastroenterol, 111, 1373-80 (1996)]. A number of monoclonal antibodies which block integrin function are currently being investigated for their therapeutic potential in human disease, and one, ReoPro, a chimeric antibody against the platelet integrin αIIbβ3 is in use as a potent anti-thrombotic agent for use in patients with cardiovascular complications following coronary angioplasty.

Integrins recognize both cell surface and extracellular matrix ligands, and ligand specificity is determined by the particular alpha-beta subunit combination of the molecule [Newman, P., *ibid*]. One particular integrin subgroup of interest involves the α4 chain which can pair with two different beta chains β1 and β7 [Sonnenberg, A., *ibid*]. The α4β1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes, eosinophils and basophils) although it is absent or only present at low levels on circulating neutrophils. α4β1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L.,

Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al,* Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between α4β1 and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al,* Nature, 356, 63, (1992); Podolsky, D. K. *et al*, J. Clin. Invest. 92, 372, (1993); Abraham, W. M. *et al,* J. Clin. Invest. 93, 776, (1994)].

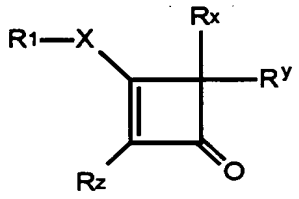
The integrin generated by the pairing of α4 and β7 has been termed LPAM-1 [Holzmann, B. and Weissman, I. L., EMBO J. 8, 1735, (1989)]. The α4β7 pairing is expressed on certain sub-populations of T and B lymphocytes and on eosinophils [Erle, D. J. *et al,* J. Immunol. 153, 517 (1994)]. Like α4β1, α4β7 binds to VCAM-1 and fibronectin. In addition, α4β7 binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue such as gastrointestinal mucosa termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. MAdCAM-1 is preferentially expressed in the gastrointestinal track. The interaction between α4β7 and MAdCAM-1 may also be important sites of inflammation outside of mucosal tissue [Yang, X.-D. *et al*, PNAS, 91, 12604, (1994)].

Regions of the peptide sequence recognized by α4β1 and α4β7 when they bind to their ligands have been identified. α4β1 seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al, ibid*] whilst α4β7 recognises a LDT sequence in MAdCAM-1 [Birskin, M. J. *et al,* J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al*, J. Biol. Chem., 269, 18668, (1994); Shorff, H. N.*et al,* Biorganic Med. Chem. Lett., 6, 2495, (1996); Vanderslice, P. *et al*, J. Immunol., 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the α4β1 binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A., *et al*, PNAS, 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is important to be able to identify selective inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of $\alpha 4$ integrins. Members of the group are able to inhibit $\alpha 4$ integrins such as $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. These compounds possess the additional advantage of good pharmacokinetic properties, especially low plasma clearance.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein

R^1 is a group $Ar^1L^2Ar^2Alk$- in which:

Ar^1 is an optionally substituted aromatic or heteroaromatic group;

L^2 is a covalent bond or a linker atom or group;

Ar^2 is an optionally substituted arylene or heteroarylene group;

and Alk is a chain

$-CH_2-CH(R)-$, $-CH=C(R)-$ or $—CH(CH_2R)—$

in which R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof;

X is an -O- or -S- atom or $-N(R^2)-$ group in which:

R^2 is a hydrogen atom or a C_{1-6}alkyl group;

R^x, R^y and R^z which may be the same or different is each an atom or group $-L^1(Alk^1)_n(R^3)_v$ in which L^1 is a covalent bond or a linker atom or group, Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain, R^3 is a hydrogen or halogen atom or group selected from $-OR^{3a}$ [where R^{3a} is a hydrogen atom or an optionally substituted straight or branched C_{1-6}alkyl group or C_{3-8}cycloalkyl group], $-SR^{3a}$, -CN or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycyclo-aliphatic, aromatic or heteroaromatic group, n is zero or the integer 1 and v is the integer 1, 2 or 3 provided that when n is zero and L^1 is a covalent bond v is the integer 1;
or R^z is an atom or group as previously defined and R^x and R^y are joined together to form an optionally substituted spiro linked cycloaliphatic or heterocycloaliphatic group;
and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto ($CH_2C=O$)-enol (CH=CHOH) tautomers. Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

Optionally substituted aromatic groups represented by Ar^1 when present in the group R^1 include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Optionally substituted heteroaromatic groups represented by the group Ar^1 when present in the group R^1 include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic

fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, [2,3-dihydro]benzothienyl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, e.g. 2,6-naphthyridinyl, or 2,7-naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, iso-quinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydro-isoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Each aromatic or heteroaromatic group represented by the group Ar^1 may be optionally substituted on any available carbon or, when present, nitrogen atom. One, two, three or more of the same or different substituents may be present and each substituent may be selected for example from an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ in which L^3 and L^4, which may be the same or different, is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^2 is an optionally substituted aliphatic or heteroaliphatic chain and R^4 is a hydrogen or halogen atom or a group selected from optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl, $-OR^5$ [where R^5 is a hydrogen atom, an optionally substitued C_{1-6}alkyl or C_{3-8}cycloalkyl group], $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$,

$-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $N(R^5)CON(R^6)(R^7)$ [where R^7 is a hydrogen atom, an optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl group], $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^3 and L^4 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom

When L^3 and/or L^4 is present in these substituents as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$ [where R^8 is a hydrogen atom or an optionally substituted straight or branched C_{1-6}alkyl group], $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)O-$, $-ON(R^8)-$, $-N(R^8)N(R^8)-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$, or $-N(R^8)SO_2N(R^8)-$ groups. Where the linker group contains two R^8 substituents, these may be the same or different.

When R^{3a}, R^4, R^5, R^6, R^7 and/or R^8 is present as a C_{1-6}alkyl group it may be a straight or branched C_{1-6}alkyl group, e.g. a C_{1-3}alkyl group such as a methyl, ethyl or i-propyl group. C_{3-8}cycloalkyl groups represented by R^{3a}, R^4, R^5, R^6 and/or R^7 include C_{3-6}cycloalkyl groups e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C_{1-6}alkoxy e.g. methoxy or ethoxy groups.

When the groups R^5 and R^6 or R^6 and R^7 are both C_{1-6}alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom selected from -O-, -S- or $-N(R^5)-$. Particular examples of such heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When Alk^2 is present as an optionally substituted aliphatic or heteroaliphatic chain it may be any optionally substituted aliphatic or heteroaliphatic chain as described hereinafter for Alk^1.

Halogen atoms represented by R^4 in the optional Ar^1 substituents include fluorine, chlorine, bromine, or iodine atoms.

Examples of the substituents represented by $-L^3(Alk^1)_tL^4(R^4)_u$ when present in Ar^1 groups in compounds of the invention include atoms or groups $-L^3Alk^2L^4R^4$, $-L^3Alk^2R^4$, $-L^3R^4$, $-R^4$ and $-Alk^2R^4$ wherein L^3, Alk^2, L^4 and R^4 are as defined above. Particular examples of such substituents include $-L^3CH_2L^4R^4$, $-L^3CH(CH_3)L^4R^4$, $-L^3CH(CH_2)_2L^4R^4$, $-L^3CH_2R^4$, $-L^3CH(CH_3)R^4$, $-L^3(CH_2)_2R^4$, $-CH_2R^4$, $-CH(CH_3)R^4$, $-(CH_2)_2R^4$ and- R^4 groups.

Thus Ar^1 in compounds of the invention may be optionally substituted for example by one, two, three or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, and/or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{3-8}cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or $-C(OH)(CF_3)_2$, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxy-propylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, haloC_{1-6}alkyl, e.g. $-CF_3$, $-CHF_2$, CH_2F, haloC_{1-6}alkoxy, e.g. $-OCF_3$, $-OCHF_2$, $-OCH_2F$, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6} dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2R^5$ e.g. $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), $-SO_3Alk^3$, C_{1-6}alkylsulphinyl, e.g. methylsulphinyl, C_{1-6}alkylsulphonyl, e.g.

methylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6} alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkyl-aminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethyl-amino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonyl-amino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.

L^2 when present as part of the group R^1 in compounds of the invention may be a linker atom or group L^{2a} or a linker -(Alk^3)L^{2a}-, where Alk^3 is an optionally substituted aliphatic or heteroaliphatic chain which may be any such chain as described hereinafter for Alk^1, and L^{2a} may be any linker atom or group as described hereinbefore for L^3.

Optionally substituted arylene groups represented by Ar^2 when present as part of the group R^1 include those aromatic groups as previously described for Ar^1.

Optionally substituted heteroarylene groups represented by Ar^2 when present as part of the group R^1 include those heteroaromatic groups as previously described for Ar^1.

Each divalent arylene or heteroarylene group represented by Ar^2 may be attached to the remainder of the molecule through any available ring carbon or nitrogen atoms.

The arylene and heteroarylene groups represented by Ar^2 may be optionally substituted by one, two or more substituents selected from the atoms or groups $-L^3(Alk^2)_tL^4(R^4)_u$ described herein. Where two of these atoms or groups are present they may be the same or different.

When the group R is present in R^1 in compounds of the invention as a derivative of a carboxylic acid it may be for example a carboxylic acid ester or amide. Particular esters and amides include $-CO_2Alk^7$ and $-CONR^5R^6$ groups as defined herein. When R is a biostere of a carboxylic acid it may be for example a tetrazole or other acid such as phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an acylsulphonamide group.

Esters ($-CO_2Alk^7$) and amide ($-CONR^5R^6$) derivatives of the carboxylic acid group ($-CO_2H$) in compounds of formula (1) may advantageously be used as prodrugs of the active compound. Such prodrugs are compounds which undergo biotransformation to the corresponding carboxylic acid prior to exhibiting their pharmacological effects and the invention particularly extends to prodrugs of the acids of formula (1). Such prodrugs are well known in the art, see for example International Patent Application No. WO00/23419, Bodor, N. (Alfred Benzon Symposium, 1982, 17, 156-177), Singh, G. et al (J. Sci. Ind. Res., 1996, 55, 497-510) and Bundgaard, H., (Design of Prodrugs, 1985, Elsevier, Amsterdam).

Esterified carboxyl groups represented by the group $-CO_2Alk^7$ include groups wherein Alk^7 is a straight or branched optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; an optionally substituted C_{2-8}alkenyl group such as a propenyl e.g. 2-propenyl or butenyl e.g. 2-butenyl or 3-butenyl group, an optionally substituted C_{2-8}alkynyl group such as a ethynyl, propynyl e.g. 2-propynyl or butynyl e.g. 2-butynyl or 3-butynyl group, an optionally substituted C_{3-8}cycloalkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C_{3-8}cycloalkylC_{1-8}alkyl group such as a cyclopentylmethyl, cyclohexylmethyl or cyclohexylethyl group; an optionally substituted C_{3-8}heterocycloalkylC_{1-6}alkyl group such as a morpholinyl-N-ethyl, thiomorpholinyl-N-methyl, pyrrolidinyl-N-ethyl, pyrrolidinyl-N-propyl, piperidinyl-N-ethyl, pyrazolidinyl-N-methyl or piperazinyl-N-ethyl group; an optionally substituted C_{1-6}alkyloxyC_{1-6}alkyl group such as a methyloxyethyl or propyloxyethyl group; an optionally substituted C_{1-6}alkylthioC_{1-6}alkyl group such as an ethylthioethyl group; an optionally substituted C_{1-6}alkylsulfinylC_{1-6}alkyl group such as an methylsulfinylethyl group; an optionally substituted C_{1-6}alkylsulfonylC_{1-6}alkyl group such as an methylsulfonylmethyl group; an optionally substituted C_{3-8}cycloalkyloxyC_{1-6}alkyl group such as a cyclohexyloxymethyl group; an optionally substituted C_{3-8}cycloalkylthioC_{1-6}alkyl group such as a cyclopentylthiomethyl group; an optionally substituted C_{3-8}cycloalkylsulfinylC_{1-6}alkyl group such as a cyclopentylsulfinylmethyl group; an optionally substituted C_{3-8}cycloalkylsulfonylC_{1-6}alkyl group such as a cyclopentylsulfonylmethyl group; an optionally substituted C_{1-6}alkyloxycarbonylC_{1-6}alkyl group such as isobutoxycarbonylpropyl group; an optionally substituted C_{1-6}alkyloxycarbonylC_{1-6}alkenyl group such as isobutoxycarbonylpentenyl group; an optionally substituted C_{1-6}alkyloxycarbonyloxyC_{1-6}alkyl group such as an isopropoxycarbonyloxyethyl e.g a 1-(isopropoxycarbonyloxy)ethyl, 2-(isopropoxycarbonyloxy)ethyl or ethyloxycarbonyloxymethyl group; an optionally substituted C_{1-6}alkyloxycarbonyloxyC_{1-6}alkenyl group such as a isopropoxycarbonyloxybutenyl group, an optionally substituted C_{3-8}cycloalkyloxycarbonyloxyC_{1-6}alkyl group such as a cyclohexyloxycarbonyloxyethyl, e.g. a 2-(cyclohexyloxycarbonyloxy)ethyl group, an optionally substituted N-di-C_{1-8}alkylaminoC_{1-8}alkyl group such as a N-

dimethylaminoethyl or N-diethylaminoethyl group; an optionally substituted N-C_{6-12}aryl-N-C_{1-6}alkylaminoC_{1-6}alkyl group such as a N-phenyl-N-methylaminomethyl group; an optionally substituted N-di-C_{1-8}alkylcarbamoylC_{1-8}alkyl group such as a N-diethylcarbamoylmethyl group; an optionally substituted C_{6-10}arylC_{1-6}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-10}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-10}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; a C_{6-12}arylthioC_{1-8}alkyl group such as an optionally substituted phenylthioethyl group; a C_{6-12}arylsulfinylC_{1-8}alkyl group such as an optionally substituted phenylsulfinylmethyl group; a C_{6-12}arylsulfonylC_{1-8}alkyl group such as an optionally substituted phenylsulfonylmethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a acetoxymethyl, ethoxycarbonyloxyethyl, pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; an optionally substituted C_{4-8}imidoC_{1-8}alkyl group such as a succinimidomethyl or phthalamidoethyl group; a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group or a triglyceride such as a 2-substituted triglyceride e.g. a 1,3-di-C_{1-8}alkylglycerol-2-yl group such as a 1,3-diheptylglycerol-2-yl group. Optional substituents present on the Alk^7 group include R^{13a} substituents described below.

It will be appreciated that in the forgoing list of Alk^7 groups the point of attachment to the remainder of the compound of formula (1) is via the last described part of the Alk^7 group. Thus, for example a methoxyethyl group would be attached by the ethyl group, whilst a morpholinyl-N-ethyl group would be attached via the N-ethyl group.

It will be further appreciated that in the forgoing list of Alk^7 groups, where not specifically mentioned, alkyl groups may be replaced by alkenyl or alkynyl groups where such groups are as previously defined for Alk^1. Additionally these alkyl, alkenyl or alkynyl groups may optionally be interrupted by one, two or three linker atoms or groups where such linker atoms and groups are as previously defined for L^3.

When the group R^2 is present in compounds of the invention as a C_{1-6}alkyl group it may be for example a straight or branched C_{1-6}alkyl group e.g. a C_{1-3}alkyl group such as a methyl or ethyl group.

When present in the group R^x, R^y and/or R^z in compounds of formula (1) the linker atom or group represented by L^1 may be any linker atom or group as described above for the linker atom or group L^3. In addition L^1 may also be a -Se- atom.

When Alk^1 is present in the group R^x, R^y and/or R^z in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10}aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene chains.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-CH_2-$, $-(CH_2)_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-(CH_2)_2CCH-$ groups.

Heteroaliphatic chains represented by Alk^1 when present in the group R^x, R^y and/or R^z in compounds of formula (1) include the aliphatic chains just described for Alk^1 but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^5 where L^5 is as defined above for L^3 when L^3 is a linker atom or group. Each L^5 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group. Particular examples include optionally substituted $-CH_2L^5-$, $-CH_2CH_2L^5-$, $-L^5CH_2-$, $-L^5CH_2CH_2-$, $-CH_2L^5CH_2CH_2-$, $-(CH_2)_2L^5CH_2-$, $-(CH_2)_3L^5CH_2-$, $-L^5(CH_2)_3$, $-CH_2L^5CH_2CHL^5CH_2-$ and $-(CH_2)_2L^5CH_2CH_2-$ chains.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, $-CO_2H$, $-CO_2R^9$, where R^9 is an optionally substituted straight or branched C_{1-6}alkyl group as defined above for R^4, $-CONHR^9$, $-CON(R^9)_2$, $-COCH_3$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, $-S(O)R^9$, $-S(O)_2R^9$, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^9$ and $-N(R^9)_2$ groups. Where two R^9 groups are present in any of the above substituents these may be the same or different.

Optionally substituted cycloaliphatic groups represented by the group R^3 when present in the group R^x, R^y and/or R^z in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g C_{3-7} cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by the group R^3 when present in the group R^x, R^y and/or R^z include optionally substituted C_{3-10}heterocycloaliphatic groups. Particular examples include optionally substituted C_{3-10}heterocycloalkyl, e.g. C_{3-7}heterocycloalkyl, or C_{3-10}heterocycloalkenyl, e.g. C_{3-7}hetercycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^5 as defined above.

Optionally substituted polycycloaliphatic groups represented by the group R^3 when present in the group R^x, R^y and/or R^z include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group R^3 include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^5 atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocyclo-aliphatic and heteropolycycloaliphatic groups represented by the group R^3

include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1-oxide, tetrahydrothiopyran-1,1-dioxide, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups represented by the group R^3 include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, propyl or i-propyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy, ethoxy or propoxy, haloC_{1-6}alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6}alkylthio e.g. methylthio, ethylthio or propylthio, or $-(Alk^4)_gR^{10}$ groups in which Alk^4 is a straight or branched C_{1-3}alkylene chain, g is zero or an integer 1 and R^{10} is a -OH, -SH, $-N(R^{11})_2$, (in which R^{11} is an atom or group as defined herein for R^7) -CN, $-CO_2R^{11}$, $-NO_2$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-COR^{11}$, $-CSN(R^{11})_2$, $-N(R^{11})COR^{11}$, $-N(R^{11})CSR^{11}$, $-SO_2N(R^{11})_2$, $-N(R^{11})SO_2R^{11}$, $-N(R^{11})CON(R^{11})_2$, $-N(R^{11})CSN(R^{11})$, $N(R^{11})SO_2N(R^{11})_2$ or optionally substituted phenyl group. Where two R^{11} atoms or groups are present in these substituents these may be the same or different or joined to form a heterocyclic ring as previously described when R^5 and R^6 are joined together. Optionally substituted phenyl groups include phenyl substituted by one, two or three of the R^{13} groups described below

Additionally, when the group R^3 is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^6)_p(Alk^5)_qR^{12}$ in which L^6 is -C(O)-, -C(O)O-, -C(S)-, $-S(O)_2-$, $-CON(R^8)-$, $-CSN(R^8)-$ or $SO_2N(R^8)-$; p is zero or an integer 1; Alk^5 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R^{12} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

C_{1-3}alkylene chains represented by Alk^4 include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ and $-CH_2CH(CH_3)-$ chains.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk^5 include those optionally substituted chains described above for Alk^1. Optional substituents which may be present on these groups include those described above in relation to Alk^1.

Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocycloaliphatic groups represented by R^{12} include those groups just described for the group R^3. Optional substituents which may be present on those groups include those described above in relation to R^3 cycloaliphatic groups.

Aromatic or heteroaromatic groups represented by R^{12} include those groups described herein for the group Ar^1. Optional substituents which may be present on these groups include those R^{13} optional substituents described hereinafter.

When the group R^3 is an optionally substituted aromatic or heteroaromatic group it may be for example an aromatic or heteroaromatic group as described herein for the group Ar^1.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group R^3 include one, two, three or more substituents, each selected from an atom or group R^{13} in which R^{13} is $-R^{13a}$ or $-Alk^6(R^{13a})_m$, where R^{13a} is a halogen atom, or an

amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{14}$ [where R^{14} is an $-Alk^6(R^{13a})_m$, aryl or heteroaryl group], $-CSR^{14}$, $-SO_3H$, $-SOR^{14}$, $-SO_2R^{14}$, $-SO_3R^{14}$, $-SO_2NH_2$, $-SO_2NHR^{14}$ $SO_2N(R^{14})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{14}$, $-CSNHR^{14}$, $-CON[R^{14}]_2$, $-CSN(R^{14})_2$, $-N(R^{11})SO_2R^{14}$, $-N(SO_2R^{14})_2$, $-NH(R^{11})SO_2NH_2$, $-N(R^{11})SO_2NHR^{14}$, $-N(R^{11})SO_2N(R^{14})_2$, $-N(R^{11})COR^{14}$, $-N(R^{11})CONH_2$, $-N(R^{11})CONHR^{14}$, $-N(R^{11})CON(R^{14})_2$, $-N(R^{11})CSNH_2$, $-N(R^{11})CSNHR^{14}$, $-N(R^{11})CSN(R^{14})_2$, $-N(R^{11})CSR^{14}$, $-N(R^{11})C(O)OR^{14}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^{11})-$, -C(O)-, -C(S)-, S(O) or $-S(O)_2$ groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{11})SO_2NHet^1$, $-N(R^{11})CONHet^1$, $-N(R^{11})CSNHet^1$, $-SO_2N(R^{11})Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{11})-$, -C(O)- or -C(S)- groups], $-Het^2$, $-CON(R^{11})Het^2$, $-CSN(R^{11})Het^2$, $-N(R^{11})CON(R^{11})Het^2$, $-N(R^{11})CSN(R^{11})Het^2$, aryl or heteroaryl group; Alk^6 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^{15})-$ groups [where R^{15} is a hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{11} or R^{14} groups are present in one of the above substituents, the R^{11} or R^{14} groups may be the same or different.

When in the group $-Alk^6(R^{13a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on any suitable carbon atom in $-Alk^6$. Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^6$. Clearly, when m is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^6 becomes an alkyl, alkenyl or alkynyl group.

When R^{13a} is a substituted amino group it may be for example a group $-NHR^{14}$ [where R^{14} is as defined above] or a group $-N(R^{14})_2$ wherein each R^{14} group is the same or different.

When R^{13a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{14}$ or a $-SR^{14}$ or $-SC(=NH)NH_2$ group respectively.

Esterified carboxyl groups represented by the group R^{13a} include groups of formula $-CO_2Alk^8$ wherein Alk^8 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^8 group include R^{13a} substituents described above.

When Alk^6 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or $-S(O)-$, $-S(O)_2-$ or $-N(R^8)-$ groups.

Aryl or heteroaryl groups represented by the groups R^{13a} or R^{14} include mono- or bicyclic optionally substituted C_{6-12}aromatic or C_{1-9} heteroaromatic groups as described above for the group Ar^1. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When -NHet^1 or -Het^2 forms part of a substituent R^{13} each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet^1 or -Het^2 include those optional substituents described above in relation to aliphatic chains represented by Alk^1.

Particularly useful atoms or groups represented by R^{13} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, e.g. t-butyloxycarbonylpiperazinyl, pyrrolidinyl, dioxolanyl, dioxanyl, oxazolidinyl, thiazolidinyl, imidazolidinyl or piperidinyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{4-7}cycloalkyl, e.g. cyclobutyl, cyclopentyl, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino, ethylamino or propylamino, C_{6-12}arylC_{1-6}alkylamino, e.g. benzylamino, 4-fluorobenzylamino or 4-hydroxyphenylethylamino, amino (-NH_2), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, aminoC_{1-6}alkylamino, e.g. aminoethylamino or aminopropylamino, optionally substituted Het^{1}NC_{1-6}alkylamino, e.g. 3-morpholinopropylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC_{1-6}alkylamino, e.g. 2-hydroxyethylamino, 3-hydroxypropylamino or 3-hydroxybutylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO_2H), -CO_2Alk^7 [where Alk^7 is as defined above], C_{1-6} alkanoyl e.g. acetyl,

propyryl or butyryl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH_2, sulphonyl (-SO_3H), -SO_3Alk^7, C_{1-6}alkylsulphinyl, e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl or propylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl, ethylaminosulphonyl or propylaminosulphonyl C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl, ethylaminocarbonyl or propylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}alkylaminoC_{1-6}alkylaminocarbonyl, e.g. methylaminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkyl-aminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, haloC_{1-6}alkylsulphonylamino, e.g. trifluoromethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino

or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{13} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{13} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R^3.

When the groups R^x and R^y are joined together to form an optionally substituted spiro linked cycloaliphatic or heterocycloaliphatic group joined to the cyclobutenone ring as defined by formula (1) it may be any such cycloaliphatic or heterocycloaliphatic group as previously described for R^3. Optional substituents which may be present on such spiro linked cycloaliphatic or heteroaliphatic groups include those optional substituents as described in relation to R^3.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

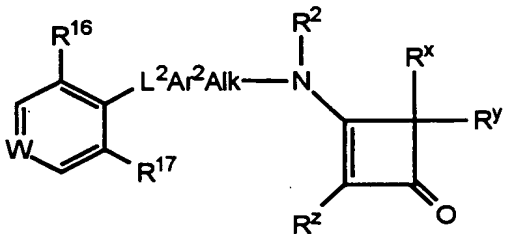
Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In the compounds according to the invention the group R^1 is preferably an $Ar^1L^2Ar^2Alk$- group. In compounds of this type Ar^1 is preferably an optionally substituted phenyl, monocyclic heteroaromatic or bicyclic heteroaromatic group. Particularly useful monocyclic heteroaromatic groups are optionally substituted five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. Particularly useful substituents present on these Ar^1 groups include halogen atoms or alkyl, haloalkyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-CO_2H$, $-CO_2CH_3$, $-NO_2$, $-N(R^5)COR^6$ or -CN groups as described above in relation to the compounds of formula (1). Particularly useful bicyclic heteroaromatic groups represented by Ar^1 include optionally substituted ten-membered fused-ring heteroaromatic groups containing one or two heteroatoms, especially nitrogen atoms. Particular examples include optionally substituted naphthyridinyl, especially 2,6-naphthyridinyl, 2,7-naphthyridinyl, quinolinyl and isoquinolinyl, especially isoquinolin-1-yl groups. Particular optional substituents include those just described for monocyclic heteroaromatic groups. Additionally, in the compounds according to the invention X is preferably an $-N(R^2)$- group.

A particularly useful group of compounds according to the invention has the formula (2a):



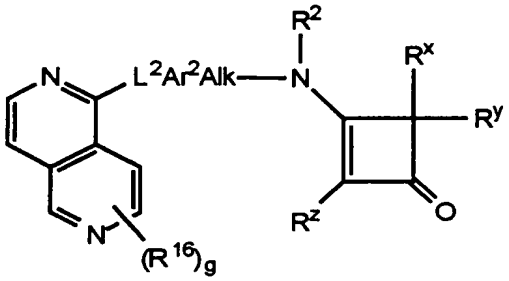
(2a)

wherein -W= is -CH= or -N=;
R^{16} and R^{17}, which may be the same or different is each a hydrogen atom or an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ in which L^3, Alk^2, t, L^4, R^4 and u are as defined previously;
L^2, Ar^2, Alk, R^2, R^x, R^y and R^z are as defined for formula (1);
and the salts, solvates, hydrates and N-oxides thereof.

-W= in compounds of formula (2a) is preferably -N= or -N(O)=. Most preferably W is -N=.

R^{16} and R^{17} in compounds of formula (2a) is each preferably as particularly described above for compounds of formula (1), other than a hydrogen atom. Particularly useful R^{16} and R^{17} substituents include halogen atoms, especially fluorine or chlorine atoms, or C_{1-6}alkyl, especially methyl, ethyl or isopropyl, haloC_{1-6}alkyl especially halomethyl, most especially $-CF_3$, $-CHF_2$ or $-CH_2F$, C_{1-6}alkoxy especially methoxy or haloC_{1-6}alkoxy especially halomethoxy, most especially $-OCF_3$, $-OCHF_2$ or $-OCH_2F$ groups.

A further particularly useful group of compounds according to the invention has the formula (2b):

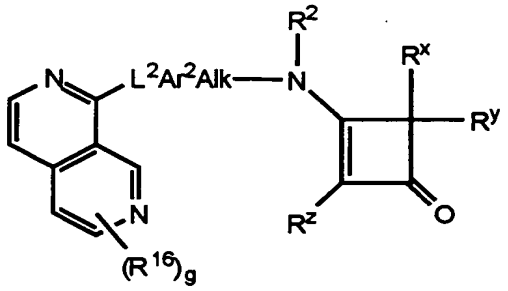


(2b)

wherein g is the integer 1, 2, 3 or 4;
R^{16}, is an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ in which L^3, Alk^2, t, L^4, R^4 and u are as defined previously;
L^2, Ar^2, Alk, R^2, R^x, R^y and R^z are as defined for formula (1);
and the salts, solvates, hydrates and N-oxides thereof.

Particularly useful R^{16} substituents when present in compounds of formula (2b) include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6}alkyl e.g. methyl, ethyl or isopropyl, haloC_{1-6}alkyl, especially halomethyl, most especially $-CF_3$, C_{1-6}alkoxyl, especially methoxy, haloC_{1-6}alkoxy, especially halomethoxy, most especially $-OCF_3$, -CN, $-CO_2CH_3$, $-NO_2$, amino ($-NH_2$), substituted amino ($-NR^5R^6$) especially $-NHCH_3$ and $-N(CH_3)_2$, $-N(R^5)COCH_3$, especially $-NHCOCH_3$ groups or optionally substituted phenyl, furyl, thienyl, imidazolyl, pyridyl and pyrimidinyl groups.

A further particularly useful group of compounds according to the invention has the formula (2c):

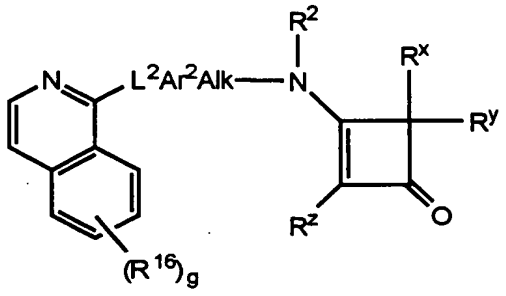


(2c)

wherein R^{16}, g, L^2, Ar^2, Alk, R^2, R^x, R^y and R^z are as defined for formula (2b);
and the salts, solvates, hydrates and N-oxides thereof.

Each R^{16} atom or group in compounds of formula (2c) may be independently selected from an atom or group $-L^3(Alk^2)_nL^4(R^4)_u$ as previously particularly defined for compounds of formula (2b).

A further particularly useful group of compounds according to the invention has the formula (2d):



(2d)

wherein R^{16}, g, L^2, Ar^2, Alk, R^2, R^x, R^y and R^z are as defined for formula (2b):
and the salts, solvates, hydrates and N-oxides thereof.

Each R^{16} atom or group in compounds of formula (2d) may be independently selected from an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ as previously defined for compounds of formula (2b).

In one preferred class of compounds of formula (2d) at least one R^{16} atom or group is present at the 3-position of the isoquinoline ring. In a preferred group of compounds of this class R^{16} is an optionally substituted phenyl ring.

It will be understood that compounds according to formulae (2a), (2b), (2c) and (2d) include, where applicable, the corresponding hydroxy tautomers.

Alk in compounds of the invention is preferably:
$-CH-$ or, especially, $-CH_2CH(R)-$.
CH_2R

In one preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R is a $-CO_2H$ group.

In another prefered class of compounds of formulae (1) and (2) R is an esterified carboxyl group of formula $-CO_2Alk^7$. In this class of compound Alk^7 is preferably a C_{1-8}alkyl group, especially a methyl, ethyl, propyl, i-propyl, butyl or pentyl group, an optionally substituted C_{3-8}cycloalkyl

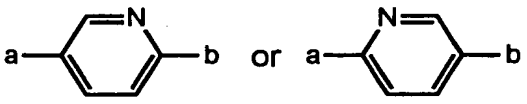
group, especially a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group, an optionally substituted C_{6-10}aryl group, especially a phenyl group, an optionally substituted C_{6-10}arylC_{1-6}alkyl group, especially a benzyl group, an optionally substituted C_{3-8}heterocycloalkylC_{1-6}alkyl group, especially a morpholinyl-N-ethyl group, an optionally substituted N-di-C_{1-8}alkylaminoC_{1-8}alkyl group, especially a N-dimethylaminoethyl or N-diethylaminoethyl group or an optionally substituted C_{1-6}alkyloxyC_{1-6}alkyl group, especially a methyloxyethyl group. Especially preferred esterified carboxyl groups include $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$ and $-CO_2CH(CH_3)_2$ groups.

In general in compounds of formula (1) when X is a $-N(R^2)$ group and in compounds of formulae (2a), (2b), (2c) and (2d) R^2 is preferably a hydrogen atom.

In compounds of formula (2a) L^2 is preferably L^{2a} where L^{2a} is a $-CON(R^8)-$ group, especially a -CONH- group or a $-(Alk^3)L^{2a}-$ group, especially a $-CH_2O-$ group.

In general in compounds of formulae (2b), (2c) and (2d) L^2 is preferably L^{2a} where L^{2a} is an -O- atom or $-N(R^8)-$ group. An especially useful $-N(R^8)-$ group is -NH-.

The group Ar^2 in compounds of formulae (1), (2a), (2b), (2c) and (2d) is preferably an optionally substituted phenylene or optionally substituted pyridinediyl group or formula:



where a and b signify the points of attachment of L^2 and Alk respectively. Most preferably Ar^2 is an optionally substituted 1,4-phenylene group.

Particularly preferred optional substituents which may be present on Ar^2 in compounds of the invention include halogen atoms, especialy fluorine,

chlorine or bromine atoms, or C_{1-6}alkyl e.g. methyl, ethyl or i-propyl, haloC_{1-6}alkyl especially halomethyl, most especialy $-CF_3$, C_{1-6}alkoxy especially methoxy or haloC_{1-6}alkoxy, especially halomethoxy, most especially $-OCF_3$, -CN, $-CO_2CH_3$, $-NO_2$, amino ($-NH_2$), substituted amino (NR^5R^6) especially $-NHCH_3$ and $-N(CH_3)_2$ and $-N(R^5)COCH_3$, especially $-NHCOCH_3$ groups.

In one generally preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x, R^y and/or R^z is an optionally substituted alkyl group, most preferably an optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, n-heptyl, or n-hexyl group. Particularly preferred optional substituents which may be present on such R^x, R^y and/or R^z alkyl groups include halogen atoms, especially fluorine or chlorine atoms, C_{1-6}alkoxy groups, especially methoxy, haloC_{1-6}alkoxy groups, especially $-OCF_3$, -CN, $-CO_2CH_3$, $-NO_2$, substituted amino ($-NR^5R^6$) especially $-NHCH_3$ and $-N(CH_3)_2$ and optionally substituted phenyl groups.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^z is a hydrogen atom.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x is a hydrogen atom.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^z is a group $-L^1(Alk^1)_nR^3$. In this class of compounds L^1 is preferably an -O-, -S-, $-N(R^8)$-, especially -NH- or $-N(CH_3)$- or -Se- linker atom or group. Most preferably L^1 is a -S- atom. R^3 is preferably an optionally substituted C_{6-12}aromatic group, most preferably an optionally substituted phenyl group or an optionally substituted C_{1-9}heteroaromatic group, preferably an optionally substituted monocyclic C_{1-9}heteroaromatic group, most preferably a 5- or 6-membered monocyclic heteroaromatic

group containing one, two or three heteroatoms selected from oxygen, sulphur or nitrogen atoms, especially an optionally substituted furyl, thienyl, pyridyl or pyrimidinyl group. Optional substituents which may be present on such aromatic and heteroaromatic groups include those substituents as described hereinbefore in relation to R^{16} substituents in compounds of formula (2a). In one preferred group of compounds of this class n is zero. In another preferred group of compounds of this class n is the integer 1 and Alk^1 is preferably an optionally substituted aliphatic chain, most preferably an optionally substituted C_{1-6}alkylene chain, especially a $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH(CH_3)-$ chain.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^z is each a hydrogen atom.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x is a hydrogen atom and R^z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom, or R^z is a group $-L^1(Alk^1)_nR^3$ as just described.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x is a hydrogen atom and R^y is an optionally substituted alkyl group as just described for generally preferred alkyl groups.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^z is each a hydrogen atom and R^y is an optionally substituted alkyl group as just described.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x is a hydrogen atom, R^z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom or R^z is a group $-L^1(Alk^1)_nR^3$ and R^y is an optionally substituted alkyl group as just described

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x is a hydrogen atom and R^y and R^z is each an optionally substituted alkyl group as just described.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^y is each an optionally substituted alkyl group as just described.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^y is each an optionally substituted alkyl group as just described and R^z is a hydrogen atom.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^y is each an optionally substituted alkyl group as just described and R^z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom, or R^z is a group $-L^1(Alk^1)_nR^3$ as just described.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x, R^y and R^z is each an optionally substituted alkyl group as just described.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^y are joined to form an optionally substituted spiro linked cycloaliphatic group particularly a C_{3-10}cycloaliphatic group, most particularly a C_{3-7}cycloalkyl group, especially an optionally substituted cyclopentyl cyclohexyl or cycloheptyl group. Particularly preferred optional substituents which may be present on such spiro linked cycloaliphatic groups include halogen atoms, especially fluorine or chlorine atoms, C_{1-6}alkyl groups, especially methyl, ethyl, propyl or i-propyl, C_{1-6}alkoxy groups, especially methoxy or ethoxy, haloC_{1-6}alkoxy groups, especially $-OCF_3$, -CN, $-CO_2CH_3$, $-NO_2$ and substituted amino ($-N(R^{11})_2$), especially $-NHCH_3$ and $-N(CH_3)_2$ groups. In another preferred group of compounds of this class R^z is an alkyl group as just described. In a further preferred group of compounds of this class R^z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom, particularly a bromine atom. In a still further preferred group of compounds of this class R^z is a group $-L^1(Alk^1)_nR^3$ as just described.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^y are joined to form an optionally substituted spiro linked heterocycloaliphatic group, particularly an optionally substituted C_{3-10}heterocycloaliphatic group, most particularly an optionally substituted C_{3-7}heterocycloalkyl group, especially an optionally substituted C_{3-7}heterocycloalkyl group containing one or two -O-, -S-, -S(O)-, $-S(O)_2$-, -NH- or -C(O)- heteroatoms or heteroatom-containing groups. Especially preferred optionally substituted heterocycloaliphatic groups include optionally substituted 5- and 6-membered heterocycloalkyl groups containing one heteroatom or heteroatom-containing group as just described, especially optionally substituted pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl tetrahydrothiopyran-1-oxide or tetrahydrothiopyran-1,1-dioxide groups. Particularly preferred optional substituents which may be present on such spiro linked heterocycloaliphatic groups include halogen atoms, especially fluorine or chlorine atoms, C_{1-6}alkyl groups, especially methyl, ethyl, propyl or i-propyl, C_{1-6}alkoxy groups, especially methoxy or ethoxy, haloC_{1-6}alkoxy groups, especially $-OCF_3$, -CN, $-CO_2CH_3$, $-NO_2$ and substituted amino ($-N(R^{11})_2$), especially $-NHCH_3$ and $-N(CH_3)_2$ groups. In addition when the spiro linked heterocycloaliphatic group contains a nitrogen atom this may be substituted by a group $-(L^6)_p(Alk^5)_qR^{12}$ where L^6 is preferably -C(O)- or $-S(O)_2$-, Alk^5 is preferably an optionally substituted C_{1-6}alkylene chain, especially a $-CH_2$-, $-(CH_2)_2$- or $-CH(CH_3)CH_2$- chain or an optionally substituted heteroC_{1-6}alkylene chain, especially $-CH_2L^5$-, $-CH_2CH_2L^5$-, $-L^5CH_2$- or $-L^5CH_2CH_2$ chain where L^5 is an -O- or -S- atom or -NH or $-N(CH_3)$- group and R^{12} is a hydrogen atom or an optionally substituted phenyl ring. In one preferred group of compounds of this class R^z is a hydrogen atom. In another preferred group of compounds of this class R^z is an alkyl group as just described. In a further preferred group of compounds of this class R^z is a halogen atom, especialy a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom. In a still further preferred group of compounds of this class R^z is a group $-L^1(Alk^1)_nR^3$ as just described.

Particularly useful compounds of the invention include:

(2S)-2-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(2,7)naphthyridin-1-yloxy]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3-methyl[2.7]naphthyridin-1-yl)oxy]phenyl}propanoate;
(2*S*)-2-[(3-Oxospiro[3.5]non-1-en-1-yl)amino]3-{4-[(3,5-dichloro-isonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(3-Oxospiro[3.6]dec-1-en-1-yl)amino]3-{4-[(3,5-dichloroiso-nicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxo-7-acetyl-7-aza-spiro[3,5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxospiro[3.6]dec-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(3-Oxo-7-acetyl-7-azaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(3-Oxo-7-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxo-7-oxaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-bromo-7-methoxy-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Phenylselenenyl-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)- 2-{[2-(Phenylsulfanyl)-4,4-dimethyl-3-oxo-1-cyclobutenyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
Ethyl (2S) 2-{[4,4-dimethyl-2-(phenylselenenyl)-3-oxo-1-cyclobutenyl] amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate;
(2S)-2-[(2-Bromo-4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Chloro-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
and the salts, solvates, hydrates, N-oxides and carboxylic acid ester, particularly methyl, ethyl, propyl and i-propyl esters thereof.

Most especially useful compounds of the invention include:

(2S)-2-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(2,7)naphthyridin-1-yloxy]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3-methyl[2.7]naphthyridin-1-yl)oxy]phenyl}propanoate;
(2*S*)-2-[(3-Oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloro-isonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(3-Oxospiro[3.6]dec-1-en-1-yl)amino]-3-{4-[(3,5-dichloroiso-nicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxospiro[3.6]dec-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(3-Oxo-7-acetyl-7-azaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-3-oxo-7-oxaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-bromo-7-methoxy-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)- 2-{[2-(Phenylsulfanyl)-4,4-dimethyl-3-oxo-1-cyclobutenyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Bromo-4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
(2S)-2-[(2-Chloro-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;
and the salts, solvates, hydrates, N-oxides and carboxylic acid ester, particularly methyl, ethyl, propyl and i-propyl esters thereof.

Compounds according to the invention are potent and selective inhibitors of $\alpha 4$ integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders including inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the

compounds for the manufacture of a medicament for treating such diseases or disorders,

Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

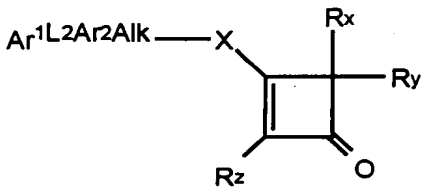
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general,

however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar^1, Ar^2, Alk, R^1, R^2, R^3, L^1, L^2, Alk^1, R^x, R^y, R^z and n when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (1a):



(1a)

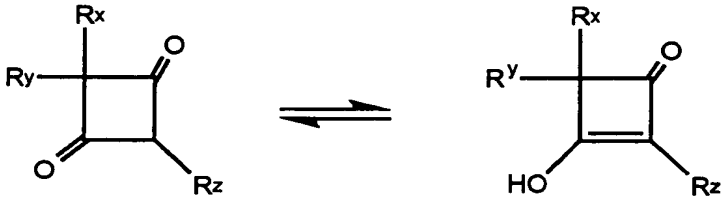
where Alk represents a group

$-CH_2CH(CO_2Alk^7)-$, $-CH=CH(CO_2Alk^7)-$, or $-CH(CH_2CO_2Alk^7)-$

[where Alk^7 is an alkyl group for example a C_{1-6}alkyl group]

The hydrolysis may be performed using either an acid or a base depending on the nature of Alk^7, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium, sodium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at a temperature from ambient to the reflux temperature. Where desired, mixtures of such solvents may be used.

According to a further aspect of the invention a compound of formula (1) may be prepared by condensation of a compound of formula (3):



(3a) (3b)

where compounds of formula (3) exist as two tautomeric isomers, (3a) and (3b) in solution with an amine of formula R^1R^2NH, an alcohol of formula R^1OH or a thiol of formula R^1SH.

The reaction may be performed in an inert solvent or mixture of solvents, for example a hydrocarbon such as an aromatic hydrocarbon e.g. benzene or toluene and/or a halogenated hydrocarbon such as 1,2-dichloroethane, or dichloromethane at a temperature from 0°C to the reflux temperature. Where necessary, for example when a salt of an amine R^1R^2NH is used, an organic base such as diisopropylethylamine can be added.

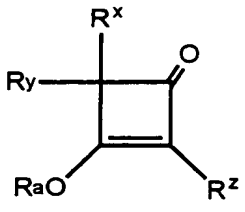
Any carboxylic acid group present in the intermediate of formula (3) or the amine R^1R^2NH, alcohol R^1OH or thiol R^1SH may need to be protected during the displacement reaction, for example as an ethyl ester. The desired acid may then be obtained through subsequent hydrolysis, for example as particularly described above and generally described below.

The displacement reaction may also be carried out on an intermediate of formula 4 (see below) under the conditions just described..

Where desired the displacement reaction may also be performed on an intermediate of formulae (3), R^1R^2NH, R^1OH or R^1SH which is linked, for example via its R, R^1 or R^3 group, to a solid support, such as a polystyrene resin. After the reaction the desired compound of formula (1) may be displaced from the support by any convenient method, depending on the original linkage chosen.

Intermediates of formulae (3) R^1R^2NH, R^1OH and R^1SH may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2a), (2b), (2c) and (2d) where appropriate functional groups exist in these compounds.

Thus intermediates of formula (3) may be obtained by hydrolysis of intermediates of formula (4):



(4)

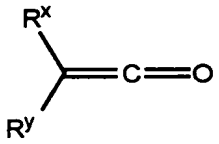
where R^a represents a C_{1-6}alkyl group or a silyl group such as a ^{t}butyldimethylsilyl group.

The hydrolysis may be performed using an acid, for example an inorganic acid such as hydrochloric acid in an organic solvent such as an ether e.g. diethylether, or an alcohol e.g. ethanol optionally in the presence of added water at a temperature from about ambient to 80°C.

Intermediates of formula (4) may be obtained by the cycloaddition of an intermediate of formula (5):

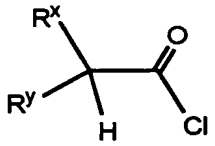
(5)

with a ketene of formula (6):



(6)

preformed or generated *in situ* during the cycloaddition reaction from an acid chloride of formula (7):



(7)

The reaction may be performed in the presence of an organic base such as an amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine such as pyridine or N-methylmorpholine optionally in an organic solvent such as an ether e.g. diethylether or diisopopylether.

Acid chlorides of formula (7) may be obtained from the corresponding acids by a convenient method of generating acid halides, for example by reaction with thionyl chloride or oxalyl chloride under such standard conditions as are well known in the art.

Compounds of formula (1a) in which R^z is for example a halogen atom may be obtained from compounds of formula (1a) in which R^z is a hydrogen atom by reaction with a halogen source such as bromine or a halosuccinamide e.g. chloro or bromosuccinamide. The reaction may be performed in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran at a temperature from about 0° to 30°. When bromine is used as halogen source the reaction may optionally be performed in the presence of added base such as an amine e.g. triethylamine.

Further compounds of formula (1a) in which R^z is a group $-L^1(Alk^1)_n(R^3)_v$ in which L^1 is for example a Se, S, O or $N(R^8)$ may be prepared by reaction of an intermediate of formula $HL^1(Alk^1)_n(R^3)_v$ with a compound of formula (1a) in which R^z is a hydrogen atom. The reaction may be performed in an organic solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran at around room temperature optionally in the presence of a base such as an amine e.g. triethylamine.

Intermediate compounds of formula (4) may also be obtained from squaric acid derivations by such well known methods in the art as those of MacDougall, J. M. *et al*, J. Org. Chem, 64 5979-83 (1999); Hergueta, R. A., J. Org. Chem., 64, 5979-83, (1999); Heileman, M. J. *et al*, J. Am. Chem. Soc. 120, 3801-2, (1998); Yamamoto, Y. *et al*, J. Org. Chem, 62, 1292-8 (1997); Zhag, D. *et al*, J. Org. Chem. 61, 2594-5 (1996); Petasis, N. A. *et al*, Synlett, 155-6 (1996); Petasis, N. A. *et al*, Tetrahedron Lett., 36, 6001-4, (1995); Turnbull, P. *et al*, J. Org. Chem 60, 644-9 (1995); Yerxa, B. R. *et al*, Tetrahedron, 50, 6173-80 (1994); Ezcurra, J. E. *et al*, Tetrahedron Lett, 34, 6177-80, (1993); Ohno, M. *et al*, Tetrahedron Lett., 34, 4807-10, (1993); Yerxa, B. R. *et al*, Tetrahedron Lett. 33, 7811-14 (1992); Xu, S. L. *et al*, J. Org. Chem, 57, 326-8 (1992) and Kravs, J .L. *et al*, Tetrahedron Lett. 28, 1765-8 (1987).

Further compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$ or $-L^2H$ group (where L^1 and L^2 is each a linker atom or group) may be treated with a coupling agent $R^3(Alk^1)_nX^1$ or

sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine, such as N-methylmorpholine or pyridine, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

Compounds of formula Ar^1X^1 may be prepared from alcohols of formula Ar^1OH by reaction with a halogenating agent, for example a phosphorous oxyhalide such as phosphorous oxychloride at an elevated temperature e.g. 110°C.

Intermediate alcohols of formula Ar^1OH in which, for example, Ar^1 represents a 2,6-naphthyridine may be prepared by methods well known to a person skilled in the art, e.g. by the method of Sakamoto,T. *et al* [Chem. Pharm. Bull. 33, 626-633, (1985)].

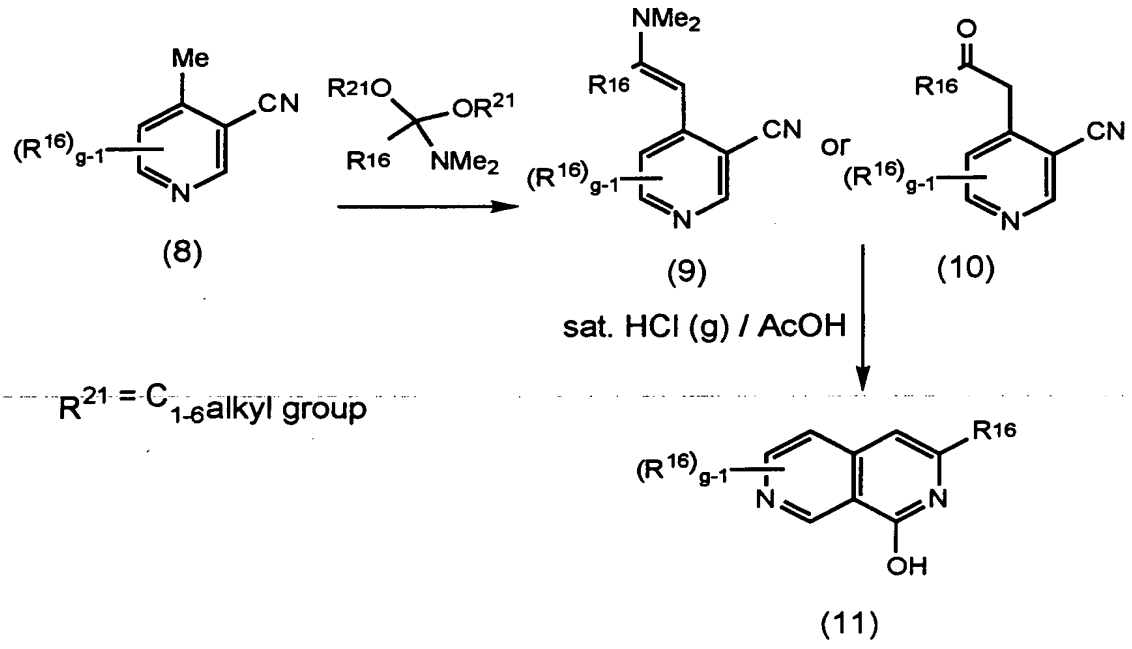
Alternatively alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a 2,6-naphthyridine may be prepared by reaction of a 2,6-naphthyridine N-oxide or N, N'-dioxide with a halogenating agent, e.g. a phosphorous oxyhalide such as phosphorous oxychloride to give a 1-halo or 1,5-dihalo-2,6-napthyridine respectively. In the case of 1,5-dihalo-2,6-napthyridines each halogen atom may be substituted separately by a reagent such as $HL^2Ar^2AlkN(R^2)H$ or $HL^3(Alk^2)_tL^4(R^4)_u$ by the particular methods just described above.

2,6-Napthyridine N-oxides and N,N'-dioxides may be generated from the corresponding 2,6-napthyridines by the general methods of synthesis of N-oxides described below or they may be synthesised by the methods of Numata, A. *et al* (Synthesis, 1999, 306-311).

Further alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a 2,6-naphthyridine, may be prepared by the methods of Giacomello G. *et al* [Tetrahedron Letters, 1117-1121 (1965)], Tan, R. and Taurins, A. [Tetrahedron Lett., 2737-2744, (1965)], Ames, D. E. and Dodds, W. D. [J. Chem. Soc. Perkin 1, 705-710 (1972)] and Alhaique, F. *et al* [Tetrahedron Lett., 173-174 (1975)].

Intermediate alcohols of formula Ar^1OH in which Ar^1 represents an optionally substituted 2,7-naphthyridin-1-yl group may be prepared by methods well known to a person skilled in the art, e.g. by the method of Sakamoto,T. *et al* [Chem. Pharm. Bull. 33, 626-633, (1985)] or Baldwin, J, J. *et al* [J. Org. Chem, 43, 4878-4880, (1978)]. Thus for example the method of Baldwin may be modified to allow the synthesis of intermediate 3-substituted 2,7-naphthyridin-1-yl groups of formula Ar^1OH as depicted in Scheme 1:

Scheme 1



Reaction of an optionally substituted 4-methyl-3-cyano pyridine of formula (8) with a N,N-dimethylformamide di-C_{1-6}alkyl acetal, e.g. N,N-dimethyl-formamide diethyl acetal, in a dipolar solvent such as an amide e.g. a

substituted amide such as dimethylformamide at an elevated temperature e.g. 140-150° gives a compound of formula (9) or (10) or a mixture thereof depending on the nature of the group R^{16}.

Compounds of formula (9) or (10) may be cyclised to 3-substituted 2,7-naphthyridin-1-yl alcohol of formula (11) by treatment with an acid e.g. an inorganic acid such as hydrochloric acid or hydrobromic acid or an acidic gas such as hydrogen chloride gas in an organic solvent e.g. an organic acid such as acetic acid optionally in the presence of water at a temperature from about ambient to 50°C.

Alternatively alkylating agents of formula Ar^1X^1 in which Ar^1 represents an optionally substituted 2,7-naphthyridin-yl group may be prepared by reaction of a 2,7-naphthyridine N-oxide or N, N'-dioxide with a halogenating agent, e.g. a phosphorous oxyhalide such as phosphorous oxychloride to give a 1-halo or 1,6-dihalo- and/or-1,8-dihalo-2,7-napthyridine respectively. In the case of 1,6-dihalo- and/or 1,8-dialo-2,6-napthyridines each halogen atom may be substituted separately by a reagent such as $HL^2Ar^2AlkN(R^2)H$ or $HL^3(Alk^2)_tL^4(R^4)_u$ by the particular methods just described above.

2,7-Napthyridine N-oxides and N,N'-dioxides may be generated from the corresponding 2,7-napthyridines by the general methods of synthesis of N-oxides described below or they may be synthesised by the methods of Numata, A. *et al* (Synthesis, 1999, 306-311).

Further alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a 2,7-naphthyridin-1-yl, may be prepared by the methods of Wenkert E. *et al* J. Am. Chem. Soc. 89, 6741-5 (1967), and Aust. J. Chem. 433 (1972), and Sheffield D.J. J. Chem. Soc. Perkin. Trans I, 2506 (1972).

Intermediate alcohols of formula Ar^1OH in which Ar^1 represents a 3-substituted isoquinolin-1-yl group may be prepared by methods well known to a person skilled in the art, e.g. by the methods of Wu M.-J. *et al* Tetrahedron, 55, 13193-200 (1999), Hiebl J. *et al* Tetrahedron Lett. 40, 7935-8 (1999), Nagarajan A. *et al* Indian J. Chem., Sect. B, 28B, 67-78

(1989), Brun E. M. *et al* Synlett, 7, 1088-90 (1999) and Brun, E. M. *et al* Synthesis, 273-280 (2000).

Further alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a isoquinolin-1-yl group, may be prepared by the methods of Falk H. *et al* Monatsch. Chem. 25, 325-33 (1994), and Deady, L. W. *et al* Aust. J. Chem 42, 1029-34 (1989).

In a further example intermediates of formula R^1R^2NH may be obtained by reaction of a compound of formula Ar^1L^2H with a compound of formula $X^1Ar^2AlkN(R^2)H$ under the reaction conditions just described

Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 2,6-naphthyridine and L^2 is a $-N(R^8)-$ group, may be prepared from substituted 4-cyano-3-cyanomethylpyridines by the methods of Alhaique, F. *et al* (*ibid* and Gazz. Chim. Ital. 1975, 105, 1001-1009) or from 3-fomylpyridines by the methods of Molina, P. at al (Tetrahedron 1992, 48, 4601-4616).

Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 2,7-naphthyridin-1-yl group and L^2 is a $-N(R^8)-$ group, may be prepared from substituted 4-formylpyridines by the methods of Molina, P. *et al* Tetrahedron, 48, 4601-4616, (1992), or by the methods described in US 3,938,367.

Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 3-substituted isoquinolin-1-yl group and L^2 is a $-N(R^8)-$ group, may be prepared by the methods of Bordner, J. *et al* J. Med. Chem. 31, 1036-9 (1988), Tovar J. D. *et al* J. Org. Chem., 64, 6499-6504 (1999), Karser E. M. *et al* Synthesis, 11, 805-6 (1974), and Molino, P *et al* J. Chem. Soc. Perkin Trans. 1 1727-31 (1990).

In another example, compounds containing a $-L^1H$ or $-L^2H$ or group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^1 is replaced by a $-C(O)X^2$, $-C(S)X^2$, $-N(R^8)COX^2$ or $-N(R^8)C(S)X^2$ group in which X^2 is a leaving atom or group as described for X^1. The

reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for example one of the alkylating agents described above in which X^1 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X^1 is replaced by a $-S(O)Hal$ or $-SO_2Hal$ group [in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a $-L^1H$ or $-L^2H$ group as defined above may be coupled with one of the alkylation agents just described but in which X^1 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups $-CO_2R^5$, $-CO_2R^{11}$ or $-CO_2Alk^7$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the groups R^5, R^{11} or Alk^7. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a

solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example, $-OR^5$ or $-OR^{14}$ groups [where R^5 or R^{14} each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{14}$ group (where R^{14} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [CO_2Alk^7 or CO_2R^5] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^5$ or $-OR^{14}$ group by coupling with a reagent R^5OH or $R^{14}OH$ in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NHR^3$ or $-NHSO_2NHAr^1$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with a sulphamide $R^3NHSO_2NH_2$ or $Ar^1NHSO_2NH_2$ in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a $-NHCSAr^1$, $-CSNHAr^1$, $-NHCSR^3$ or $-CSNHR^3$ may be prepared by treating a corresponding compound containing a $-NHCOAr^1$, $-CONHAr^1$, $-NHCOR^3$ or $-CONHR^3$ group with a thiation reagent, such as Lawesson's Reagent, in an

anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78^oC, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1 or L^2 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid,

e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In another example compounds of formula Ar^1X^1 (where X^1 is a halogen atom such as a chlorine, bromine or iodine atom) may be converted to such compounds as $Ar^1CO_2R^{20}$ (in which R^{20} is an optionally substituted alkyl, aryl or heteroaryl group), Ar^1CHO, Ar^1CHCHR^{20}, Ar^1CCR^{20}, $Ar^1N(R^{20})H$, $Ar^1N(R^{20})_2$, for use in the synthesis of for example compounds of formula $Ar^1L^2Ar^2AlkN(R^2)H$, using such well know and commonly used palladium mediated reaction conditions as are to be found in the general reference texts *Rodd's Chemistry of Carbon Compounds*, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), *Fieser and Fieser's Reagents for Organic Synthesis,* Volumes 1-19 (John Wiley and Sons, 1999), *Comprehensive Heterocyclic Chemistry*, Ed. Katritzky *et al*, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), *Comprehensive Organic Functional Group Transformations*, Ed. Katritzky *et al*, Volumes 1-7, 1995 (Pergamon), *Comprehensive Organic Synthesis*, Ed. Trost and Flemming, Volumes 1-9, (Pergamon, 1991), *Encyclopedia of Reagents for Organic Synthesis,* Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), *Larock's Comprehensive Organic Transformations* (VCH Publishers Inc., 1989) and *March's Advanced Organic Chemistry* (John Wiley and Sons, 1992).

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

NMM - N-methylmorpholine;
MeOH - methanol;
DCM - dichloromethane;
DIPEA - diisopropylethylamine;
Pyr - pyridine;
DMSO - dimethylsulphoxide;
Et_2O - diethylether;
THF - tetrahydrofuran,
FMOC - 9-fluorenylmethoxycarbonyl;
EtOAc - ethyl acetate;
BOC - butoxycarbonyl;
AcOH - acetic acid;
EtOH - ethanol;
Ar - aryl;
iPr - isopropyl;
Me - methyl;
DMF - N,N-dimethylformamide;

DBU - 1,8-Diazabicyclo[5,4-0]undec-7-ene

All NMR's were obtained either at 300MHz or 400MHz.

INTERMEDIATE 1

(+/-) 3-Ethoxy-4-methyl-4-propyl- 2-cyclobuten-1-one.

The title compound was prepared using a modification of the method of Wasserman, H.H. *et al* [J. Org. Chem, 38, 1451-1455, (1973)]; to a solution of 2-methyl pentanoyl chloride (3.91ml) and ethyl ethynylether (5g, 40% solution in hexanes, 28.6mmol) in Et_2O (35ml) at room temperature was added triethylamine (9.9ml), with stirring. The reaction was warmed to 50° and stirred for 72h prior to cooling and filtration. The filtrate was concentrated *in vacuo* and the residual oil chromatographed (SiO_2; hexanes 80: EtOAc 20) to give the title compound as a colourless oil (3.71g, 17.9mmol, 77%). δ H ($CDCl_3$, 300K), 4.84 (1H, s), 4.24-3.98 (2H, m), 2.04 (3H, s), 1.56-1.43 (4H, m), 1.30-1.26 (3H, m), 0.91 (3H, t, J 7.3Hz). m/z (ES+, 70V) 178.1 (MH^+).

INTERMEDIATE 2

(+/-) 3-Hydroxy-4-methyl-4-propyl- 2-cyclobuten-1-one

Intermediate 1 (1g, 59.5mmol) and conc. hydrochloric acid (2ml) were stirred vigorously at room temperature for 48h. The resulting slurry was filtered and the residue washed with water (3 x10ml) and dried under vacuum to give the title compound as an off-white powder (620mg, 44.2mmol, 74%). δH ($CDCl_3$, 300K) 3.79 (2H, s), 1.59-1.53 (2H, m), 1.41-1.27 (2H, m), 1.18 (3H, s), 0.85 (3H, t, J 7.3Hz). m/z (ES+, 70V) 140.9 (MH^+).

INTERMEDIATE 3

3-Ethoxy-4,4-dipropyl-2-cyclobuten-1-one.

The title compound was prepared using a modification of the method of Wasserman, H.H. *et al*, [J. Org. Chem, 38, 1451-1455, (1973)]; triethylamine (29ml) was added dropwise at room temperature to a well-stirred solution of di-n-propylacetyl chloride (13.9g, 85.8mmol) and ethyl ethynylether (15g, 40% solution in hexanes, 85.7mmol) in toluene (120ml. The reaction was warmed to 60° and stirred for 48h prior to cooling and

filtration. The filtrate was concentrated *in vacuo* and the residual oil chromatographed (SiO_2; hexanes 80: EtOAc 20) to give the title compound as a brown oil (11.2g, 57.1mmol, 67%). δH ($CDCl_3$, 300K) 5.02 (1H, s), 4.32 (2H, q, J 7.1Hz), 1.69-1.61 (4H, m), 1.45-1.40 (4H, m), 1.02 (6H, t, J 7.3Hz). m/z (ES^+, 70V) 197.1 (MH^+).

INTERMEDIATE 4

3-Hydroxy-4,4-dipropyl-2-cyclobuten-1-one

Intermediate 3 (10.2mmol) and 6M hydrochloric acid (10ml) were stirred vigorously at 65° for 72h. The resulting slurry was diluted with DCM (30ml) and distilled water (30ml) and extracted with DCM (3x10ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a pale yellow oil, which crystallised on standing (1.49g, 8.87mmol, 87%).

INTERMEDIATE 5

3-Ethoxy-2-hexyl-4,4-dimethyl-2-cyclobuten-1-one.

The title compound was prepared using a modification of the method of Wasserman, H.H. *et al,* [J. Org. Chem, 38, 1451-1455, (1973)]; triethylamine (22ml) was added dropwise at room temperature to a well-stirred solution of isobutyryl chloride (7.3ml, 69mmol) and 1-ethoxy-1-octyne [prepared according to the method of Kocienski, P. *et al.* Tetrahedron Lett. 1833, 30, (1989)] (6.5g, 63mmol) in diethylether (100ml). The reaction was warmed to 35° and stirred for 96h prior to cooling and filtration. The filtrate was concentrated *in vacuo* and the residual oil chromatographed (SiO_2; hexanes 80: EtOAc 20) to give the title compound as a brown oil (8.6g, 38mmol, 61%). δH ($CDCl_3$, 300K) 4.34 (2H, d, J 7.1Hz), 2.05 (2H, dd, J 5.6Hz 7.3Hz), 1.44 (3H, t, J 7.1Hz), 1.27-1.12 (8H, m), 1.23 (6H, s), 0.89 (3H, t, J 2.7Hz). m/z (ES^+, 70V) 225.0 (MH^+).

INTERMEDIATE 6

2-Hexyl-3-hydroxy-4,4-dimethyl-2-cyclobuten-1-one.

Intermediate 5 (7.6g, 34.0mmol) and 6M hydrochloric acid (10ml) were stirred vigorously at 100° for 18h. The resulting slurry was diluted with DCM (30ml) and distilled water (30ml) and extracted with DCM (3 x10ml).

The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was triturated with hexanes and filtered to give the title compound as an off-white powder (6.5g, 33.0mmol, 98%). δ H ($CDCl_3$, 300K) 2.01 (2H, t, J 7.0Hz), 1.49-1.44 (2H, m), 1.34-1.19 (14H, m), 0.89-0.84 (3H, m). m/z (ES^+, 70V) 197.0 (MH^+).

INTERMEDIATE 7

(+/-) 4-Benzyl-3-ethoxy-4-methyl-2-cyclobuten-1-one

The title compound was prepared using a modification of the procedure of Wasserman *et al* [J. Org. Chem, 38, 1451-1455, (1973)]; triethylamine (20ml) was added to a stirred solution containing α-methyl tetrahydrocinnamoyl chloride (5g, 27.5mmol) and ethyl ethynylether (6g, 40% soln. in hexanes, 85.7mmol) and the resulting slurry heated to 35° for 3d. The crude reaction mixture was then filtered and the residue concentrated *in vacuo*. The residual oil was chromatographed (SiO_2, EtOAc 20: hexanes 80) to give the title compound as a pale brown oil (4.91g, 86%). δ H ($CDCl_3$, 300K) 7.19-7.05 (5H, m), 4.56 (1H, s), 4.09-4.00 (1H, m), 3.97-3.89 (1H, m), 2.86 (1H, d, J 14.0Hz), 2.86 (1H, d, J 14.0Hz), 1.30 (3H, t, J 7.1Hz), 1.24 (3H, s). m/z (ES^+, 70V) 216.9 (MH^+).

INTERMEDIATE 8

(+/-) 4-Benzyl-3-hydroxy-4-methyl-2-cyclobuten-1-one.

Intermediate 7 (4.5g, 20.9mmol) and hydrochloric acid (6M, 10ml) were stirred at room temperature for 48h. Filtration of the resulting slurry and washing of the residue with water (3 x 15ml) gave the title compound as a pale brown powder (3.92g, 20.8mmol, 99%). δH ($CDCl_3$, 300K) 7.03-6.83 (5H, m), 4.24 (1H, s), 2.52 (2H, s), 0.94 (3H, s). m/z (ES^+, 70V) 189.1 (MH^+).

INTERMEDIATE 9

3-Cyanopyridinyl-4-(2-(*N,N*-dimethylamino)ethylen-1-yl)

A solution of 4-methyl-3-cyanopyridine [prepared acccording to Ref: J. Prakt. Chem. 338, 663 (1996)], (8.0g, 67.8mmol) and *N,N*-dimethylformamide diethyl acetal (11.0g, 74.8mmol) in dry DMF (50ml) was stirred at 140° under N_2 for 2 days. An additional portion of N,N,-dimethylformamide diethyl acetal (5g) was added and stirred at 140° for

4h. The volatiles were removed *in vacuo* and the obtained dark oil partitioned between EtOAc (300ml) and water (50ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 100ml). The combined organic extracts were washed with brine (30ml), dried (Na_2SO_4), treated with activated charcoal, filtered and evaporated *in vacuo* to afford essentially pure title compound as a dull orange solid (10.1g, 85%). δH ($CDCl_3$) 8.49 (1H, s), 8.25 (1h, d, J 5.9hz), 7.29 (1H, d, J 13.2Hz), 7.09 (1H, d, J 5.9Hz), 5.25 (1H, d, J 13.2Hz) and 2.99 (6H, s); m/z (ES$^+$, 70V) 174 (MH^+).

INTERMEDIATE 10

1-Hydroxy-2,7-naphthyridine hydrochloride salt

HCl gas was bubbled through a stirred solution of Intermediate 9 (6.2g, 3.58mmol) in glacial acetic acid (50ml) and water (0.64ml, 3.55mmol) for 1-2min. The reaction mixture was stirred in a stoppered flask at 40° for 18h. The volatiles were removed *in vacuo* affording a dark residue, which was treated with water (3 x 20ml) and re-evaporated *in vacuo*. The obtained dark semi-solid was treated with 40ml warm ethanol, ice-cooled, and the undissolved solid collected by filtration affording the title compound as a green coloured solid (5.2g, 80%) δH (DMSO-d^6) 12.5 (1H, br s), 9.38 (1H, s), 8.84 (1H, d, J 7.0Hz), 8.15 (1H, d, J 7.0Hz), 7.89 (1H, br dd, J 7.0, 5.0Hz) and 6.85 (1H, d, J 7.0Hz); m/z (ES$^+$, 70V), 147 (MH^+).

INTERMEDIATE 11

1-Chloro-2,7-naphthyridine

Intermediate 10 (5.2g, 28.5mmol) was stirred with phosphorous oxychloride (75ml) at 110° for 24h. The volatiles were removed *in vacuo* affording a dark oil which was poured into an ice-bath cooled mixture of saturated aqueous $NaHCO_3$ (100ml containing 20g solid $NaHCO_3$) and EtOAc (100ml). After thorough mixing the phases were separated and the aqueous layer re-extracted with EtOAc (2 x 75ml). The combined organic extracts were washed with brine (15ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a yellow solid (4.0g, 85%) δH ($CDCl_3$) 9.45 (1H, s), 8.81 (1H, d, J 5.7Hz), 8.47 (1H, d, J 5.7Hz), 7.66 (1H, d, J 5.7Hz) and 7.60 (1H, d, J 5.7Hz); m/z (ES$^+$, 70V) 165 and 167 (MH^+).

INTERMEDIATE 12

Ethyl (2S)-2-amino-3-[4-(2,7-naphthyridin-1-ylamino)phenyl] propanoate

A solution of ethyl-(*S*)-3-[4-aminophenyl]-2-[*t*-butoxycarbonylamino] propanoate (638mg, 2.07mmol) and Intermediate 11 (310mg, 1.88mmol) in ethoxyethanol (2ml) was stirred at 120° for 15 min and at 100° for 1h under nitrogen. The volatiles were removed *in vacuo* and the dark residue partitioned between EtOAc (70ml) and saturated aqueous $NaHCO_3$ (10ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford a dark foam. Chromatography (SiO_2; 5 to 10% MeOH/DCM) afforded a mixture of ethyl-(*S*)-3-[4-(2,7-naphthyridin-1-ylamino)phenyl]-2-[(*t*-butoxycarbonyl) amino]propanoate and some of the title compound (730mg). This mixture was treated with a solution of trifluoroacetic acid (5ml) and DCM (5ml) at room temperature for 1h. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (75ml) and saturated aqueous $NaHCO_3$ (20ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford an orange solid. Chromatography (SiO_2; 10% MeOH/DCM) afforded the title compound as a straw-coloured solid (420mg, 60% over two steps). δH ($CDCl_3$) 10.70 (1H, s), 10.31 (1H, s), 9.44 (1H, d, J 5.6Hz), 8.94 (1H, d, J 5.6Hz), 8.55 (1H, d, J 7.3Hz), 8.54 (2H, d, J 8.5Hz), 8.46 (1H, d, J 5.6Hz), 7.94 (2H, d, J 8.5Hz), 4.84 (2H, q, J 7.1Hz), 4.35 (1H, t, J 6.6Hz), 4.10 (2H, br s), 3.64 (1H, dd, J 13.5, 6.4Hz), 3.56 (1H, dd, J 13.5, 7.0Hz) and 1.95 (3H, t, J 7.1Hz); m/z (ES+, 70V) 337 (MH^+).

INTERMEDIATE 13

Methyl (2S)-2-amino3-[4-(2,7-naphthyridin-1-yloxy)phenyl]propanoate

A mixture of *N*-(BOC)-(*S*)-tyrosine methyl ester (1.71g, 5.80 mmol) potassium carbonate (0.80g, 5.80mmol) and Intermediate 11 (1.0g, 6.08mmol) in dry DMF (10ml) was stirred at room temperature for 18h, and at 40° for 18h. The DMF was removed *in vacuo* and the residue partitioned between EtOAc (80ml) and 10% aqueous Na_2CO_3 (20ml). The

phases were separated and the aqueous layer re-extracted with EtOAc (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford a new colourless oil. Chromatography (silica; 2.5% MeOH/DCM) afforded reasonably pure *N*-t-butoxycarbonyl protected title compound (1.75g, 71%). This material was dissolved in EtOAc (40ml) and HCl gas was bubbled through the stirred solution for 1min. then the mixture was stirred for an additional 0.5h. The volatiles were removed *in vacuo* affording a yellow solid which was partitioned between EtOAc (80ml) and saturated aqueous $NaHCO_3$ (20ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained oil was chromatographed (SiO_2; 5% MeOH/DCM) to afford the title compound as a near colourless oil (0.83g, 62%) δH ($CDCl_3$) 9.77 (1H, s), 8.75 (1H, d, J 5.8Hz), 8.10 (1H, d, J 5.8Hz), 7.58 (1H, d, J 5.8Hz), 7.29 (2H, d, J 8.4Hz), 7.25 (1H, d, J 5.9Hz), 7.21 (2H, d, J 8.4Hz), 3.80-3.70 (1H, obscured m), 3.72 (3H,s), 3.15 (1H, dd, J 13.6, 5.1Hz), 2.88 (1H, dd, J 13.6, 8.0Hz) and 0.78 (2H, br s); m/z (ES+, 70V) 324 (MH^+).

INTERMEDIATE 14

4-Acetonyl-3-cyanopyridine

A solution of 4-methyl-3-cyanopyridine (4g, 33.9mmol) and *N,N*-dimethylacetamide dimethylacetyl (5.4g, 40.6mmol) in dry DMF (20ml) was stirred at 130° for 7h. The volatiles were removed *in vacuo* to afford a dark oil which solidified on standing. This material was chromatographed (SiO_2; 50% EtOAc/ Hexane - 100% EtOAc) affording the title compound as an off-yellow solid (3.73g, 69%). δH ($CDCl_3$) 8.87 (1H, s), 8.74 (1H, d, J 5.2Hz), 7.28 (1H, d, J 5,2Hz), 4.00 (2H, s) and 2.36 (3H, s); m/z (ES+, 70V) 161 (MH^+).

INTERMEDIATE 15

1-Hydroxy-3-methyl-2,7-naphthyridine hydrochloride

HCl gas was bubbled through a stirred solution of Intermediate 14 (3.73g, 23.3mmol) in glacial acetic acid (40ml) for several minutes. The flask was stoppered and reaction stirred for 18h at ambient temperature. The volatiles were removed *in vacuo* affording a straw-coloured solid. This

was twice treated with water (30ml portions) and re-evaporated *in vacuo* to dryness, affording the title compound (contaminated with ~25% unidentified by-product) as a dark straw coloured solid (4.1g). δH (DMSO-d^6) 12.46 (1H, br s), 9.32 (1H,s), 8.71 (1H, d, J 6.5Hz), 7.98 (1H, d, J 6.5Hz), 6.67 (1H,s) and 2.38 (3H, s); m/z (ES+, 70V) 161 (MH^+). Used without further purification.

INTERMEDIATE 16

1-Chloro-3-methyl-2,7-naphthyridine

Intermediate 15 (4.1g) was treated with phosphorus oxychloride (50ml) at 130° for 3h, affording a dark solution. The volatiles were removed *in vacuo* and the obtained dark oil extracted with Et_2O (100ml). Saturated aqueous $NaHCO_3$ (ice cold; containing 10g additional solid $NaHCO_3$) was poured (with CARE!) onto the crude product with swirling and ice-bath cooling. After thorough shaking, addition Et_2O (80ml) was added, the mixture re-shaken, and the phases separated. The aqueous layer was re-extracted with Et_2O (2 x 80ml) and the combined ethereal extracts washed with brine (20ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford an orange solid (3.6g). Chromatography (silica; 70% EtOAc/Hexane - 100% EtOAc) afforded a more-polar by-product (3-methyl-1H-pyrano[3,4-C]pyridin-1-one, (0.7g) and the title compound as a white solid (2.82g, 79% from intermediate 7) δH ($CDCl_3$) 9.66 (1H, s), 8.73 (1H, d, J 5.8hz), 7.56 (1H, d, J 5.8Hz), 7.40 (1H, s) and 2,69 (3H, s); m/z (ES+, 70V) 179 and 181 (MH^+).

INTERMEDIATE 17

Ethyl-(2*S*)-2-[(*tert*butoxycarbonyl)amino]-3-{4-[(3-methyl[2,7-naphthyridin-1-ylamino]phenyl}propanoate hydrochloride

Acetylchloride (55mg, 50ml, 0.70mmol) was added to absolute ethanol (25ml) and stirred for one minute. Intermediate 16 (2.50g, 14.0mmol) and ethyl-(*S*)-3-[4-aminophenyl]-2-{*tert*-butyloxycarbonyl]propanoate (4.31g, 14.0mmol) were added and the reaction mixture stirred at 60° for 2.75h. The volatiles were removed *in vacuo* to afford a yellow-orange solid. This was treated with EtOAc (~25ml), warmed, re-cooled and the precipitate collected by filtration, with Et_2O washing, affording the title compound as a yellow solid (4.96g, 73%). δH ($CDCl_3$) 10.44 (1h, br s), 10.33 (1H, br s),

8.60 (1H, d, J 6.5Hz), 8.00 (1H, d, J 6.5Hz), 7.85 (2H, d, J 8.5Hz), 7.28 (1H, d, J 8.0Hz), 7.23 (2H, d, J 8.5Hz), 7.16 (1H,s), 4.19-4.01 (1H, m), 4.08 (2H, q, J 7.0Hz), 2.97 (1H, dd, J 13.8, 5.4 Hz), 2.86 (1H, dd, J 13.8, 10.0Hz), 2.50 (3H,s), 1.34 (9H, s) and 1.15 (3H, t, J 7.0Hz); m/z (ES^+, 70V) 451 (MH^+).

INTERMEDIATE 18

Ethyl-(2*S*)-2-amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)amino] phenyl}propanoate

HCl gas was bubbled through a stirred solution of Intermediate 17 (4.95g, 10.2mmol) for 1-2min. After 30min stirring at ambient temperature the volatiles were removed *in vacuo* affording a yellow powder. This was treatd with saturated aqueous $NaHCO_3$ (30ml) then extracted with EtOAc (100ml, and 3 x 50ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* affording the title compound as a yellow solid (3.56, 100%). δH ($CDCl_3$) 9.25 (1H, s), 8.50 (1H, d, J 5.6Hz), 7.66 (2H, d, J 8.4Hz), 7.35 (1H, d, J 5.6Hz), 7.34 (1H, masked s), 7.14 (2H, d, J 8.4Hz), 6.81 (1H, s), 4.12 (2H, q, J 7.2Hz), 3.65 91H, dd, J 7.8, 5.2Hz), 3.02 (1H, dd, J 13.7, 5.2Hz), 2.80 (1H, dd, J 13.7, 7.8Hz), 2.48 (3H, s), 1.56 (2H, br s) and 1.21 (3H, t, J 7.2Hz); m/z (ES^+, 70V) 351 (MH^+).

INTERMEDIATE 19

Ethyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

A mixture of *N-t*-butyloxycarbonyl-(*S*)-tyrosine ethyl ester (14.5g, 46.9mmol), caesium carbonate (14.05g, 43.1mmol) and Intermediate 9 (7.0g, 39.2mmol) in dry DMF (60ml) was stirred at room temperature for 48h. The reaction was diluted with Et_2O (150ml) and filtered off. The filtrate was evaporated under high vacuum and the residue was chromatographed (SiO_2; 40% - 60% EtOAc/Hexane) which afforded the title compound as a viscous, straw-coloured oil (16.2g, 77%) δH ($CDCl_3$) 9.56 (1H, s), 8.58 (1H, d, J 5.8Hz), 7.39 (1H, d, J 5.8Hz), 7.15-7.10 (4H, m), 7.00 (1H, s), 4.99-4.91 (1H,m), 4.54-4.46 (1H, m), 4.09 (2H, q, J 7.1Hz), 3.10-2.99 (2H,m), 2.36 (3H, s), 1.34 (9H, s) and 1.15 (3H, t, J 7.1Hz); m/z (ES^+, 70V) 452 (MH^+).

INTERMEDIATE 20

Ethyl (2S)-2-amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl} propanoate

HCl gas was bubbled through a stirred solution of Intermediate 19 (16g) in EtOAc (300ml) until a persistent fine white precipitate formed (~2minutes). After stirring for 0.5h the volatiles were removed *in vacuo*. The obtained solid was partitioned between EtOAc (250ml) and saturated aqueous $NaHCO_3$ (80ml plus 5g solid $NaHCO_3$). The phases were separated and the aqueous layer re-extracted with EtOAc (5 x 50ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford an oil. Chromatography (SiO_2; 100% EtOAC - 10% EtOH/EtOAc) afforded the title compound as a viscous oil (11.1g, 89%). δH ($CDCl_3$) 9.71 (1H,s), 8.70 (1H, d, J 5.Hz), 7.50 (1H, d, J 5.8Hz), 7.31-7.28 (4H,m), 7.11 (1H, s), 4.23 (2H, q, J 7.1Hz), 3.79-3.72 (1H, m), 3.14 (1H, dd, J 14.1, 5.4Hz), 2.94 (1H, dd, J 14.1, 7.8Hz), 2.47 (3H, s), 1.75-1.50 (2H, br s) and 1.30 (3H, t, J 7.1Hz); m/z (ES^+, 70V) 352 (MH^+).

INTERMEDIATE 21

1-Chloro-2,6-naphthyridine

1-Hydroxy-2,6-naphthyridine (550mg) [prepared according to the method of Sakamoto, T. *et al* Chem. Pharm. Bull. 33, 626, (1985)] was stirred with phosphorous oxychloride (10ml) at 110° for 5h. The volatiles were removed *in vacuo* and the residue treated carefully with ice. After diluting with water (to ~25ml), solid $NaHCO_3$ was added to effect neutralisation and the product extracted into EtOAc (2 x 80ml). The combined organic extracts were dried ($MgSO_4$), evaporated *in vacuo*, and the crude product chromatographed (SiO_2; EtOAc) affording the title compound as a slightly yellow solid (420mg, 68%). δH ($CDCl_3$) 9.35 (1H, s), 8.82 (1H, d, J 5.9Hz), 8.48 (1H, d, J 5.6Hz), 8.00 (1H, d, J 5.9Hz), 7.74 (1H, d, J 5.6Hz); m/z (ES^+, 70V) 165 and 167 (MH^+).

INTERMEDIATE 22

Ethyl (2S)-2-[(*tert*-butoxycarbonyl)amino]3-[4-([2,6]naphthyridin-1-ylamino)phenyl]propanoate

Ethyl (*S*)-3-(4-aminophenyl)-2-[N-(t-butyloxycarbonyl)amino]propanoate (600mg, 1.95mmol), Intermediate 21 (350mg, 2.13mmol) and DIPEA (276mg, 372µl, 2.13mmol) in 2-ethoxyethanol (0.5ml) were stirred at 130° under N_2 for several hours. The reaction was partitioned between EtOAc (70ml) and saturated aqueous $NaHCO_3$ (30ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were washed with brine (10ml), dried ($MgSO_4$) and evaporated *in vacuo* to afford a dark oil. Chromatography (SiO_2; 3% MeOH/DCM) gave the title compound as a dull orange foam (360mg, 42%). δH ($CDCl_3$) 9.19 (1H, s), 8.67 (1H, d, J 5.9Hz), 8.24 (1H, d, J 5.8Hz), 7.66 (1H, d, J 5.9Hz), 7.65 (2H, d, J 8.5Hz), 7.21 (1H, d, J 5.8Hz), 7.16 (2H, d, J 8.5Hz), 7.15 (1H, obscured s), 5.05-4.97 (1H, m), 4.60-4.51 (1H, m), 4.19 (2H, q, J 7.1Hz), 3.17-3.04 (2H, m), 1.44 (9H, s), 1.27 (3H, t, J 7.1Hz); m/z (ES$^+$, 70V) 459 (MNa^+), 437 (MH^+).

INTERMEDIATE 23

Ethyl (2*S*)-2-amino-3-[4-([2,6]naphthyridin-1-ylamino)phenyl] propanoate

Intermediate 22 (360mg) was treated with a solution of trifluoroacetic acid (10ml) and DCM (10ml) and stirred at RT for 2h. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (80ml) and saturated aqueous $NaHCO_3$ (30ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound as a dark orange viscous oil (280mg, 100%). δH ($CDCl_3$) 9.18 (1H, s), 8.66 (1H, d, J 5.9Hz), 8.22 (1H, d, J 5.8Hz), 7.67 (1H, d, J 5.9Hz), 7.64 (2H, d, J 8.5Hz), 7.22 (2H, d, J 8.5Hz), 7.19 (1H, d, J 5.8Hz), 4.20 (2H, q, J 7.1Hz), 3.73 (1H, dd, J 7.9, 5.1Hz), 3.10 (1H, dd, J 13.6, 5.2Hz), 2.87 (1H, dd, J 13.6, 7.9Hz), 1.70 (3H, br s), 1.28 (3H, t, 7.1Hz); m/z (ES$^+$, 70V) 337 (MH^+).

INTERMEDIATE 24

Methyl (2*S*)-2-(*t*-butoxycarbonyl)amino]-3-[4-([2,6]naphthyridin-1-yloxy)phenyl]propanoate

To *N*-(*t*-butyloxycarbonyl)-(*S*)-tyrosine methyl ester (1.42g, 4.82mmol) in dry DMF (10ml) was added Intermediate 21 (0.79g, 4.82mmol) and cesium carbonate (1.65g, 5.06 mmol) and the reaction stirred at 45° under N_2 for 2 days. The DMF was evaporated, EtOAc added and washed (3x) with water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed (SiO_2; 40 to 100% EtOAc/isohexane) to afford the title compound as white foam (1.61g, 82%). δH ($CDCl_3$) 9.29 (1H, s), 8.76 (1H, d, J 5.74HZ), 8.17 (1H, d, J 5.74Hz), 8.11 (1H, d, J 5.8Hz), 7.43 (1H, d, J 5.8Hz), 7.22-7.18 (3H, m), 5.03 (1H, br s), 4.61 (1H, br s), 3.75 (3H, s), 3.15-3.05 (2H, m), 1.44 (9H, s); m/z (ES^+, 70V) MH^+ 424.

INTERMEDIATE 25

3,5-Dichloropyridine-4-carboxylic acid

A solution of 3,5-dichloropyridine (5.00g, 33.8mmol) in THF (25ml) was added to a solution of LDA [generated from nBuLi (2.5M solution in hexanes, 14.9ml, 37.2mmol) and diisopropylamine (4.10g, 5.7ml, 40.6mmol)] in THF (25ml) at -78° under nitrogen, to give a yellow/brown slurry. The reaction was stirred for 30min at -78° then CO_2 gas was bubbled through to give a clear brown solution that slowly gave a precipitate, warmed to RT over 2h, then quenched with water (20ml) and partitioned between Et_2O (100ml) and 1M NaOH (100ml). The aqueous layer was separated and acidified to pH1 with concentrated hydrochloric acid and then extracted with 10% MeOH in DCM (100ml x 3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under vacuum to give a brown solid that was recrystallised from ethanol and dried under vacuum to give the title compound as pinkish crystals (2.63g, 41%). δH (DMSO-d^6) 8.74 (2H, s). δC (DMSO-d^6) 163.5, 147.7, 141.0, 126.7

INTERMEDIATE 26

Ethyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

A slurry of the compound of Intermediate 25 (51.2g, 0.267mol) in DCM (195ml) and thionyl chloride (195ml, 2.67mol) was treated with DMF (5 drops) and heated to reflux for 4h. The reaction was concentrated *in vacuo* and azeotroped with toluene (2 x 50ml) to give a yellow solid which

was used without further purification. A solution of ethyl-(*S*)-3-(4-aminophenyl)-2-(t-butoxycarbonyl amino)propionate (130.8g, 0.425mol) in DCM (800ml) was cooled to 0° and treated with NMM (56.0ml, 0.51mol), stirred for 5 minutes and then a solution of the acid chloride (98.3g, 0.468mol) in DCM (200ml) was added dropwise keeping the reaction temperature below 5°. The reaction was stirred for 1h, quenched with $NaHCO_3$ solution (500ml), the organic layer separated, washed with $NaHCO_3$ solution (500ml), 10% citric acid solution (500ml) and $NaHCO_3$ solution (500ml), dried ($MgSO_4$)and concentrated *in vacuo* to give a yellow solid which was recrystallised (EtOAc/hexane) to give the title compound, (140g, 69%). δH (DMSO d^6), 8.8 (2H, s), 7.55 (2H, d, J 8.5Hz), 7.23 (2H, d, J 8.5Hz), 4.0 (3H, m), 3.4 (2H, b s), 2.9 (1H, m), 2.8 (1H, m), 1.3 (9H, s), 1.25 (3H, t). m/z (ES^+, 70V) 504 (MNa^+).

INTERMEDIATE 27

Ethyl (2S)-2-amino-3-{4-[(3,5-dichloroisonicotinoyl)amino] phenyl}propanoate hydrochloride

A solution of the compound of Intermediate 26 (70g, 0.146mol) in EtOAc (500ml) and 1,4-dioxan (50ml) was treated with a solution of HCl in EtOAc (500ml, 3M), and stirred at room temperature for 4h. The reaction was concentrated *in vacuo* to give a yellow solid which was triturated with Et_2O then recrystallised (EtOAc/hexane) to give the title compound (59.3g, 92%). δH (DMSO d^6), 11.10 (1H, s), 8.70 (2H, s), 7.55 (2H, d, J 8.4Hz), 7.25 (2H, d, J 8.4Hz), 4.10 (3H, m), 3.10 (2H, m), 1.10 (3H, m). m/z (ES^+, 70V) 382 (MH^+).

INTERMEDIATE 28

3-Ethoxy-7-oxaspiro[3.5]non-2-en-1-one

Tetrahydropyranyl-4-carboxylic acid (14.7g, 0.11mol) and DMF (0.5ml) in DCM (150ml) was treated dropwise with oxalyl chloride (1.1eq, 10.9ml, 0.12mol). After 1h the reaction mixture was concentrated *in vacuo* and the residual slurry was diluted with Et_2O (200ml) and the resulting precipitate removed by filtration. The filtrate was treated with ethoxyacetylene (40%w/w solution in hexanes, 1.3eq, 18ml) followed dropwise with triethylamine (25ml, 0.19mol) and the reaction stirred for 11d. Filtration and concentration of the filtrate *in vacuo* followed by chromatography

(SiO_2, 5:1 EtOAc:hexanes) gave the title compound as a pale yellow oil (12.1g, 59%). δH ($CDCl_3$, 300K) 4.85 (1H, s), 4.23 (2H, q, J 7.1Hz), 3.89-3.75 (4H, m), 1.88-1.79 (4H, m), 1.47 (3H, t, J 7.1Hz). m/z (ES+, 70V) 182.9 (MH^+).

INTERMEDIATE 29

7-Oxaspiro[3.5]nonane-1,3-dione

Intermediate 28 (12.1g, 0.67mol) and 2M hydrochloric acid (26ml) were stirred vigorously for 24h at room temperature. The resulting solution was concentrated to dryness and the residual slurry was washed with Et_2O (25ml) to give the title compound as an off-white powder (8.93g, 0.062mol). δH (DMSO d^6 300K) 4.80 (2H, s), 3.78 (4H, t, J 5.5Hz), 2.62 (4H t J 5.5Hz). m/z (ES+, 70V) 154.9 (MH^+).

INTERMEDIATE 30

3-Ethoxyspiro[3.6]decan-1-one.

A solution of cycloheptyl carbonyl chloride (10.0g, 0.062mol) and ethoxyacetylene (40%w/w solution in hexanes, 6.0g, 0.083mol, 12ml) in diethylether (50ml) was treated dropwise with triethylamine (20ml, 0.14mol) and the reaction stirred for 5d at room temperature. Filtration and concentration of the filtrate *in vacuo* followed by chromatography (SiO_2, 5:1 EtOAc:hexanes) gave the title compound as a pale yellow oil (10.5g, 0.054mol, 87%). δH ($CDCl_3$, 300K) 4.78 (1H, s), 4.20 (2H, q J 7.1Hz), 1.94-1.87 (2H, m), 1.83-1.77 (2H, m), 1.71-1.66 (2H, m), 1.63-1.52 (6H, m), 1.45 (3H, t J 7.1Hz). m/z (ES+, 70V) 194.9 (MH^+).

INTERMEDIATE 31

Spiro[3.6]decane-1,3-dione.

Intermediate 30 (8.5g, 0.044mol) and 2M hydrochloric acid (30ml) was stirred vigorously for 24h at room temperature. The resulting slurry was extracted with EtOAc (3 x 100ml), the extracts combined and concentrated *in vacuo*, and the resulting solid was recrystallised from diethyl ether to give the title compound as an off-white powder (7.1g, 0.043mol, 95%). δH (DMSO d^6, 300K) 4.58 (2H, s), 1.75-1.29 (12H, m). m/z (ES+, 70V) 166.9 (MH^+).

INTERMEDIATE 32

7-Acetyl-3-ethoxy-7-azaspiro[3.5]non-2-en-1-one.

A solution of 1-acetyl piperidine-4-carbonyl chloride (5.0g, 26.4mmol) and ethoxyacetylene (4.0g, 55.5mmol) in THF (60ml) was treated dropwise with triethylamine (7.6ml, 55.0mmol). The resulting slurry was stirred at room temperature for 5d prior to filtration and concentration of the filtrate *in vacuo*. Chromatography (SiO_2, 100% EtOAc to 95:5 EtOAc : MeOH gave the title compound as a white powder (3.97g, 17.8mmol, 67%). δH ($CDCl_3$, 300K) 4.79 (1H, s), 4.17 (2H, q, J 7.1Hz), 3.87-3.81 (1H, m), 3.56-3.42 (3H, m), 2.02 (3H, s), 1.85-1.67 (4H, m), 1.39 (3H, t 7.1Hz). m/z (ES^+, 70V) 223.9 (MH^+).

INTERMEDIATE 33

7-Acetyl-7-azaspiro[3.5]nonane-1,3-dione.

Intermediate 32 (700mg, 0.31mmol) and hydrochloric acid (2M, 5ml) were stirred at room temperature for 4h. Concentration of the resulting straw-coloured solution in vacuo gave the title compound as a pale brown water-soluble powder (535mg, 0.027mmol, 87%). m/z (ES^+, 70V) 195.9 (MH^+).

INTERMEDIATE 34

3-Ethoxy-7-methoxyspiro[3.5]non-2-en-1-one

Was prepared from 4-methoxy cyclohexanecarbonyl chloride (10g, 52.1mmol) and ethoxyacetylene (7.5g, 0.10mol) according to the method of Intermediate 1 to give the title compound as an approx. 1:1 mixture of isomers, as a pale yellow oil (7.2g, 34.4mmol, 65%). δH ($CDCl_3$, 300K) 4.81-4.79 (1H, s), 4.22-4.20 (2H q, J 7.1Hz), 3.34-3.32 (3H, s), 3.31-3.22 (1H, m), 2.04-1.56 (8H, m), 1.44-1.43 (3H t, J 7.1Hz). m/z (ES^+, 70V) 211.0 (MH^+).

INTERMEDIATE 35

7-Methoxyspiro[3.5]nonane-1,3-dione

Intermediate 34 (5.0g, 23.9mmol) and hydrochloric acid (2M, 20ml) were stirred at room temperature for 18h. The resulting slurry was then diluted with water (50ml) and extracted with EtOAc (3 x 25ml), the extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Recrystallisation from diethylether gave the title compound as an off-white powder (4.06g,

22.4mmol, 94%). δH ($CDCl_3$, 300K) 3.81 (2H, s), 3.25 (4H, m) 1.96-1.90 (2H, m), 1.86-1.79 (2H, m), 1.73-1.66 (2H, m), 1.64-1.56 (2H, m). m/z (ES^+, 70V) 182.9 (MH^+).

EXAMPLE 1

Ethyl (2*S*)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-[4-([2,7]naphthyridin-1-yloxy)phenyl]propanoate

A solution of 3-hydroxy-4,4-dimethyl-2-cyclobutenone (57mg, 0.51mmol) [prepared according to the method of Wasserman, H.H. *et al* J. Org. Chem, 38, 1451-1455, (1973)] and the ethyl ester prepared according to the method used to prepare Intermediate 13 (164mg, 0.51mmol), in 1,2-dichloroethylene (5ml), was stirred at room temp. for 72h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO_2; EtOAc) affording the title compound as a white solid (188mg, 0.45mmol, 89%). δH ($CDCl_3$, 300K) 9.92 (1H, s), 8.75 (1H, d, J 5.7Hz), 8.60 (1H, d, J 8.6Hz), 8.04 (1H, d, J 5.8Hz), 7.82 (1H, d, J 5.6Hz), 7.47 (1H, d, J 5.8Hz), 7.27 (2H, d, J 8.5Hz), 7.16 (2H, d, J 8.5Hz), 4.31 (1H, s), 4.30-4.21 (1H, m), 3.68-3.63 (2H, q, J 7.1Hz), 3.17 (1H, dd, J 13.6, 9.4Hz), 2.95 (1H, dd, J 5.0, 13.6Hz), 1.01 (3H, s), 0.93 (3H, s). m/z (ES^+, 70V) 418.1(MH^+).

EXAMPLE 2

(2S)-2-[(4,4-Dimethyl-3-oxo-1-cyclobutenyl)amino]-3-[4-([2,7]naphthyridin-1-yloxy)phenyl]propanoic acid

The compound of Example 1 (127mg, 0.31mmol) in THF (5ml) was treated in a single portion with $LiOH.H_2O$ (13mg, 0.32mmol) in H_2O (1ml) and the reaction stirred at room temperature for 2h. The reaction was then quenched by the addition of HOAc (glacial, 1ml) and the volatiles removed *in vacuo*. Water (10ml) was then added to the residual foam and stirred vigorously to effect precipitation. The precipitate was then collected by vacuum filtration and the residue washed with water (2 x 5ml). Drying under vacuum gave the title compound as a fine white solid (108mg, 0.27mmol, 88%). δH (DMSO d^6, 300K) 9.67 (1H, s), 8.78 (1H, d, J 5.7Hz), 8.51 (1H, d, J 8.6Hz), 8.09 (1H, d, J 5.8Hz), 7.86 (1H, d, J 5.6Hz), 7.50 (1H, d, J 5.7Hz), 7.21 (2H, d, J 8.4Hz), 4.17 (2H, d, J 8.4Hz), 4.34 (1H, s), 4.18-4.14 (1H, m), 3.21 (1H, dd, J 4.9, 13.9Hz), 2.98 (1H, dd, J 13.9, 9.3Hz), 1.06 (3H, s), 0.99 (3H, s). m/z (ES^+, 70V) 404.1 (MH^+),

EXAMPLE 3

Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-[4-([2,6]naphthyridin-1-ylamino)phenyl]propanoate

A solution of 3-hydroxy-4,4-dimethyl-2-cyclobutenone (58mg, 5.1mmol) and Intermediate 23 (1.01g, 2.7mmol) in DCM (15ml), was stirred at room temperature for 48h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO_2; EtOAc) affording the title compound as a white powder (990mg, 2.3mmol, 88%). δH ($CDCl_3$, 300K) 9.33 (1H, s), 9.24 (1H, s), 8.69 (1H, d, J 5.9Hz), 8.63 (1H, d, J 8.5Hz), 8.42 (1H, dd, J 5.9, 0.8Hz), 8.15 (1H, dd, J 5.7, 1.3Hz), 7.85-7.80 (3H, m), 7.31-7.22 (4H, m), 4.39 (1H, s), 4.24-4.21 (1H, m), 4.17 (2H, q, J 7.1Hz), 3.15 (1H, dd, J 13.8, 5.6Hz), 3.00 (1H, dd, J 13.8, 9.0Hz), 1.19 (3H, t, J 7.1Hz), 1.11 (3H, s), 1.05 (3H, s). m/z (ES$^+$, 70V) 431.1 (MH^+).

EXAMPLE 4

(2S)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-[4-([2,6]naphthyridin-1-ylamino)phenyl]propanoic acid

The compound of Example 3 (500mg, 1.16mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (421mg, 1.04mmol, 90%). δH (DMSO d^6, 300K) 9.21 (1H, s), 9.12 (1H, s br), 8.66 (1H, d, J 5.8Hz), 8.38 (1H, d, J 5.8Hz), 8.18 (2H, m), 7.81 (2H, d, J 7.9Hz), 7.27 (2H, d, J 7.9Hz), 7.26 (1H, obscured s), 4.36 (1H, s), 4.13-4.07 (1H, m), 3.20 (1H, dd, J 14.0, 5.1Hz) 3.02 (1H, dd, J 41.0, 8.7Hz), 1.13 (3H, s), 1.09 (3H, s). m/z (ES$^+$, 70V) 403.0 (MH^+).

EXAMPLE 5

Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

A solution of 3-hydroxy-4,4-dimethyl-2-cyclobutenone (58mg, 0.52mmol) [prepared according to the method of Wasserman, H.H. *et al* J. Org. Chem, 38, 1451-1455, (1973)] and the free base of Intermediate 27 (200mg, 5.2mmol), in DCM (5ml), was stirred at room temperature for 48h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO_2; EtOAc) to give the title compound as a white solid (230mg, 0.48mmol, 93%). δH ($CDCl_3$, 300K) 8.48 (2H, s), 8.10 (1H, s), 7.51

(2H, d, J 8.2Hz), 7.04 (2H, d, 8.2Hz), 5.91 (1H, s), 4.43 (1H, s), 4.22 (2H, q, J 7.1Hz), 3.17 (1H, dd, J 14.0, 5.1H z), 3.05 (1H, dd, J 14.0, 5.8Hz), 1.28 (3H, t, J 7.1Hz), 1.15 (3H, s), 1.14 (3H, s). m/z (ES$^+$, 70V) 476.0 and 478.0 (MH$^+$).

EXAMPLE 6

(2*S*)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 5 (100mg, 0.21mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (76mg, 0.17mmol, 81%). δH (DMSO d ^{6}, 350K) 10.5 (1H, s), 8.74 (2H, s), 7.80 (1H, broad s), 7.53 (2H, d, J 8.1Hz), 7.25 (2H, d, J 8.1Hz), 7.26 (1H, obscured s), 4.30 (1H, s), 3.88 (1H, m), 3.16 (1H, dd, J 13.5, 4.9Hz), 3.01 (1H, dd, J 13.5, 3.8Hz), 1.11 (3H, s), 1.07 (3H, s). m/z (ES$^+$, 70V) 448.0 and 449.9 (MH$^+$).

EXAMPLE 7

Methyl (2*S*)-2-[(4*R,S*)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

A solution of Intermediate 2 (187mg, 1.33mmol) and Intermediate 20 (450mg, 1.2mmol), in chloroform (10ml), was stirred at 55° for 48h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO_2; EtOAc) to give the title compound as a white solid (539mg, 1.17mmol, 91%) as an approx. 1:1 mixture of diastereomers. δ H ($CDCl_3$, 300K) 9.69 (1H, s), 8.69 (1H, d, J 5.7Hz), 7.51 (1H, dd, J 9.3, 0.5Hz), 7.19-7.11 (4H, m), 5.79 (1H, d, J 7.3Hz), 4.64 (1H, s), 4.36-4.30 (1H, m), 3.84 and 3.82 (3H, s, diastereomeric CH_3), 3.31-3.15 (2H, m), 2.45 (3H, s), 1.59-1.54 (1H, m), 1.50-14 (1H, m), 1.34-1.23 (2H, m), 1.28 and 1.27 (3H, s, diastereomeric CH_3), 0.91-0.86 (3H, m). m/z (ES$^+$, 70V) 460.1 (MH$^+$).

EXAMPLE 8

(2*S*)-2-[(4*R,S*)-4-Methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoic acid

The compound of Example 7 (230mg, 0.5mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (198mg, 0.44mmol, 79%) as an approx. 1:1 mixture of

diastereomers. δH (DMSO d^6, 300K) 13.0 (1H, s), 9.60 (1H, d, J 9.7Hz), 8.72 (1H, d, J 5.6Hz), 8.49-8.43 (1H, m NH), 7.76 (1H, d, J 4.7Hz), 7.41-7.34 (2H, m), 7.27-7.21 (2H, m), 4.47 and 4.43 (1H, s), 4.19-4.13 (1H, m), 3.29-3.23 (3H, s, and 1H as obscured m), 3.02-2.97 (1H, m), 2.36 and 2.35 (3H, s), 1.50-1.10 (4H, m), 1.08 and 0.98 (3H, s), 0.84-0.63 (3H, m), m/z (ES^+, 70V) 446.1 and 447.1 (MH^+).

EXAMPLE 9

Ethyl (2*S*)-2-[(4,4-dipropyl-3-oxo-1-cyclobutenyl)amino]-3-[4-([2,7]naphthyridin-1-yloxy)phenyl]propanoate

A solution of Intermediate 4 (180mg, 1.07mmol) and the ethyl ester of Intermediate 13 (362mg, 1.07mmol), in chloroform (7ml), was stirred at room temperature for 96h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO_2; EtOAc) to give the title compound as a white solid (406mg, 0.83mmol, 78%). δH ($CDCl_3$, 300K) 9.72 (1H, s), 8.71 (1H, d J 5.7Hz), 8.04 (1H, d, J 5.8Hz), 7.55 (1H, d, J 5.7Hz), 7.22-7.16 (4H, m), 5.67 (1H, d, J 7.9Hz), 4.64 (1H, s), 4.26-4.16 (3H, m), 3.20 (1H, dd, J 14.1, 5.7Hz), 3.11 (1H, dd, J 14.1, 6.6Hz), 1.58-1.01 (8H, m), 0.81 (6H, t, J 7.0Hz). m/z (ES^+, 70V) 488.1 and 489.1 (MH^+).

EXAMPLE 10

(2*S*)-2-[(3-Oxo-4,4-dipropyl-1-cyclobutenyl)amino]3-[4-([2,7]naphthyridin-1-yloxy)phenyl]propanoic acid

The compound of Example 9 was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine off-white powder (35mg, 0.07mmol, 19%). δ H (DMSO d^6, 350K) 9.68 (1H, s), 8.83 (1H, d, J 5.7Hz), 8.37 (1,d, J 8.5Hz), 8.14 (1H, d, J 5.8Hz), 7.91 (1H, d, J 5.7Hz), 7.55 (1H, d, J 5.8Hz), 7.39 (2H, d, J 8.4Hz), 7.28 (2H, d, J 8.4Hz), 4.53 (1H, s), 4.14 (1H, dd, J 9.8, 4.3Hz), 3.25 (1H, dd, J 14.0, 4.6Hz), 3.0 (1H, dd, J 10.3, 14.0Hz), 1.50-0.64 (14H, m). m/z (ES^+, 70V) 460.1 and 461.1 (MH^+).

EXAMPLE 11

Ethyl (2*S*)-2-[(4*R,S*)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-([2,7]naphthyridin-1-yloxy)phenyl]propanoate

A solution of Intermediate 2 (300mg, 2.1mmol) and the ethyl ester of Intermediate 13 (724mg, 2.14mmol), in DCM (15ml), was stirred at room temperature for 24h. The reaction was then diluted with DCM (30ml) and distilled water (20ml) and washed successively with 1M aqueous hydrochloric acid (30ml) water (30ml) and saturated, aqueous sodium hydrogen carbonate (30ml). The organic layer was then dried ($MgSO_4$), filtered and concentrated *In vacuo*. The residual foam was chromatographed (SiO_2; EtOAc) to give the title compound as a white powder (827mg, 1.8mmol, 84%) as an approx. 1:1 mixture of diastereomers. δH ($CDCl_3$, 300K) 9.72 (1H, s), 8.71 (1H, d, J 5.7Hz), 8.04 (1H, d, J 5.8Hz), 7.55 (1H, d, J 5.7Hz), 7.22-7.12 (5H, m), 5.80 (1H, d, J 7.6Hz), 4.57 (1H, s), 4.28-4.20 (3H, m), 3.25-3.07 (2H, m), 1.57-1.21 (7H, m), 1.18 and 1.17 (3H, s) 0.84-0.78 (3H, m). m/z (ES^+, 70V) 460.1 (MH^+) and 482.0 (MNa^+).

EXAMPLE 12

(2S)-2-[(4*R,S*)-4-Methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-([2,7]naphthyridin-1-yloxy)phenyl]propanoic acid

The compound of Example 11 (600mg, 1.31mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (520mg, 1.21mmol, 92%) as an approx. 1:1 mixture of diastereomers. δH (DMSO d^6, 300K) 9.61 and 9.58 (1H, s), 8.72 (1H, d, J 5.7Hz), 8.39-8.33 (1H, m NH), 8.04-8.00 (1H, m), 7.80-7.79 (1H, m), 7.45-7.33 (1H, m), 7.32-7.25 (2H, m), 7.18-7.12 (2H, m), 4.37 and 4.32 (1H, s), 4.10-4.04 (1H, m), 3.17-3.12 (1H, m), 2.94-2.82 (1H, m), 1.41-0.86 (4H, m), 0.99 and 0.91 (3H, s) 0.73 and 0.63 (3H, t, J 7.2Hz). m/z (ES^+, 70V) 432.0 (MH^+).

EXAMPLE 13

Ethyl (2S)-2-[(4*R,S*)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-([2,6]naphthyridin-1-ylamino)phenyl]propanoate

Prepared from Intermediate 2 (200mg, 1.43mmol) and Intermediate 23 (400mg, 1.19mmol), in a similar manner to the compound of Example 11 to give the title compound as an approx. 1:1 mixture of diastereomers as a white powder (482mg, 1.05mmol, 89%). δH ($CDCl_3$, 300K) 9.13 (1H, s), 8.61 (1H, d, J 5.9Hz), 8.17 (1H, d, J 5.8Hz), 7.66-7.60 (3H, m), 7.19-7.04

(5H, m), 5.62 (1H, t, J 4.6Hz), 4.51 and 4.49 (1H, s), 4.25-4.19 (3H, m), 3.16-3.05 (2H, m), 1.51-1.16 (7H, m), 0.85-0.77 (3H, m). m/z (ES+, 70V) 459.1 (MH^+).

EXAMPLE 14

(2*S*)-2-[(4*R,S*)-4-Methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-([2,6]naphthyridin-1-ylamino)phenyl]propanoic acid

The compound of Example 13 (600mg, 1.31mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a pale yellow powder (521mg, 1.21mmol, 95%) (approx. 1:1 mixture of diastereomers). δH (DMSO d^6, 300K) 9.10 (1H, s), 8.55-8.53 (1H, m), 8.37 and 8.31 (1H, m NH), 8.27 (1H, d, J 5.9Hz), 7.72-7.65 (2H, m), 7.15-7.08 (3H, m), 4.30 and 4.25 (1H, s), 3.99-3.94 (1H, m), 3.06-2.99 (1H, m), 2.83-2.76 (1H, m), 1.34-0.96 (4H, m), 0.94 and 0.86 (3H, s), 0.68 and 0.55 (3H, t, J 7.0Hz). m/z (ES^+, 70V) 431.0 (MH^+).

EXAMPLE 15

Ethyl (2*S*)-2-[(4*R,S*)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Prepared from Intermediate 2 (120mg, 0.86mmol) and the free base of Intermediate 27 (300mg, 0.79mmol), in a similar manner to the compound of Example 11 to give title compound as an approx. 1:1 mixture of diastereomers as a white powder (318mg, 0.63mmol, 80%). δ H ($CDCl_3$, 300K) 8.56 (2H, s), 8.29 and 8.24 (1H, s NH), 7.61-7.59 (2H, m), 7.16-7.10 (2H, m), 5.82 -5.78 (1H, m), 4.56 (1H, s), 4.32-4.26 (3H, m), 3.29-3.23 (1H, m), 3.16-3.09 (1H, m), 1.59-1.13 (7H, m), 0.89-0.84 (3H, m). m/z (ES^+, 70V) 504.0 and 506.0 (MH^+).

EXAMPLE 16

(2*S*)-2-[(4*R,S*)-4-Methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 15 (300mg, 0.59mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (261mg, 0.55mmol, 92%) (approx. 1:1 mixture of diastereomers). δ H (DMSO d^6, 300K) 10.90 (1H, s), 8.81 (2H, s), 7.60-7.56 (2H, m), 7.31-7.26 (2H, m), 4.45 and 4.42 (1H, s), 4.15-4.41 (1H, m),

3.23-3.14 (1H, m), 2.99-2.89 (1H, m), 1.49-1.12 (3H, m), 1.07 and 0.99 (3H, s), 0.84-0.54 (4H, m). m/z (ES$^+$, 70V) 476.0 and 478.0 (MH^+).

EXAMPLE 17

Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Prepared from Intermediate 6 (200mg, 1.0mmol) and the free base of Intermediate 27 (200mg, 0.52mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (201mg, 0.42mmol, 72%). δH ($CDCl_3$, 300K) 8.99 (1H, s), 8.42 (2H, s), 7.52 (2H, d, J 8.4Hz), 7.02 (2H, d, J 7.6Hz), 5.54 (1H, s), 4.34 (1H, s), 4.19 (2H, q, J 7.1Hz), 3.07 (2H, br s), 1.95-1.81 (2H, br s), 1.27-0.77 (17H, m). m/z (ES$^+$, 70V) 560.0 and 562.0 (MH^+).

EXAMPLE 18

(2S)-2-[(4,4-Dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 17 (80mg, 0.14mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as an off-white powder (62mg, 0.12mmol, 82%). δH (DMSO d^6, 300K) 10.53 (1H, s), 8.73 (2H, s), 7.60-7.56 (2H, m), 7.57 (2H, d, J 8.4Hz), 7.30 (2H, d, J 8.4Hz), 4.14-4.12 (1H, m), 3.17 (1H, dd, J 13.9, 4.8Hz), 3.03 (1H, dd, J 13.0, 9.1Hz), 1.87 (2H, t, J 7.3Hz), 1.41-1.25 (9H, m), 1.15-0.86 (8H, m). m/z (ES$^+$, 70V) 532.0 and 534.0 (MH^+).

EXAMPLE 19

Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-[4-([2,7]naphthyridin-1-yloxy)phenyl] propanoate

Prepared from Intermediate 6 (200mg, 1.0mmol) and the ethyl ester of Intermediate 13 (200mg, 0.59mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (201mg, 0.42mmol, 72%). δH ($CDCl_3$, 300K) 9.72 (1H, s), 8.71 (1H, d, J 5.7Hz), 8.03 (1H, d, J 5.8Hz), 7.56-7.51 (1H, m), 7.27-7.17 (4H, m), 5.41 (1H, br m), 4.39 (1H, br m), 4.19 (2H, q, J 7.1Hz), 3.15-3.12 (2H, m), 1.91-1.75 (2H, m), 1.39-1.09 (18H, m), 0.81-0.74 (2H, m). m/z (ES$^+$, 70V) 516.1 (MH^+).

EXAMPLE 20

(2S)-2-[(4,4-Dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-[4-([2,7]naphthyridin-1-yloxy)phenyl]propanoic acid

The compound of Example 19 (200mg, 0.39mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (161mg, 0.33mmol, 85%). δ H (DMSO d^6, 360K) 9.62 (1H, s), 8.74 (1H, d, J 5.6Hz), 8.04 (1H, d, J 5.6Hz), 7.82 (1H, d, J 5.6Hz), 7.47 (1H, d, J 5.5Hz), 7.30 (2H, d, J 8.3Hz), 7.17 (2H, d, J 8.3Hz), 4.02 (1H, br s), 3.21-3.18 (1H, m), 2.97-2.91 (1H, m), 1.74 (2H, m), 1.12-0.62 (17H, m). m/z (ES$^+$, 70V) 488.1 (MH^+).

EXAMPLE 21

Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

Prepared from Intermediate 6 (200mg, 1.0mmol) and Intermediate 18 (300mg, 0.85mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (331mg, 0.63mmol, 73%). δH ($CDCl_3$, 300K) 9.70 (1H, s), 8.70 (1H, d, J 5.8Hz), 7.51 (1H, d, J 5.8Hz), 7.26-7.19 (4H , m), 5.34 (1H, br s), 4.45 (1H, br s), 4.26 (2H, q, J 7.2Hz), 3.21 (2H, br s), 2.44 (3H, s), 2.10-1.90 (2H, m), 1.47-1.43 (2H, m), 1.33-1.12 (12H, m), 0.87-0.84 (3H, m). m/z (ES$^+$, 70V) 530.1 (MH^+).

EXAMPLE 22

(2S)-2-[(4,4-Dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoic acid

The compound of Example 21 (60mg, 0.11mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (42mg, 0.08mmol, 74%). δH (DMSO d^6, 360K) 9.59 (1H, s), 8.70 (1H, d, J 5.7Hz), 7.70 -7.68 (1H, m), 7.66 (1H, d, J 9.7Hz), 7.37 (2H, d, J 8.6Hz), 7.31 (1H, s), 7.23 (2H, d, J 8.6Hz), 4.18-4.16 (1H, m), 3.24 (1H, dd, J 13.9, 4.4Hz), 3.04 (1H, dd, J 13.9, 9.9Hz), 2.38 (3H, s), 1.86 (2H, t, J 7.3Hz), 1.38-1.19 (8H, m), 1.04 (3H, s), 0.99 (3H, s), 0.83-0.79 (3H, m). m/z (ES$^+$, 70V) 502.1 (MH^+).

EXAMPLE 23

Ethyl (2*S*)-2-[(4*R,S*)-4-benzyl-4-methyl-3-oxo-1-cyclobutenyl]amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

Prepared from Intermediate 8 (200mg, 1.0mmol) and Intermediate 20 (300mg, 0.85mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (412mg, 0.79mmol, 92%) as an approx. 1:1 mixture of diastereomers. δH ($CDCl_3$, 300K) 9.70 (1H, d, J 4.9Hz), 8.71 and 8.70 (1H, d, J 5.8Hz), 7.51 (1H, d, J 5.8Hz), 7.31-7.08 (11H, m), 5.88-5.82 (1H, m), 4.60 and 4.50 (1H, s), 4.33-4.28 (1H, m), 4.26-4.16 (2H, m), 3.25-3.07 (2H, m), 2.98-2.83 (2H, m), 2.45 and 2.40 (3H, s), 1.35-1.21 (6H, m). m/z (ES^+, 70V) 522.1 (MH^+).

EXAMPLE 24

(2*S*)-2-[(4*R,S*)-4-Benzyl-4-methyl-3-oxo-1-cyclobutenyl]amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoic acid

The compound of Example 23 (250mg, 0.48mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (221mg, 0.45mmol, 94%) as an approx. 1:1 mixture of diastereomers. δH (DMSO d^6 , 360K) 9.72 (1H, m), 8.81 (1H, m), 8.03 (1H, m), 7.82-7.77 (1H, br m), 7.46-7.20 (9H, m), 4.49 and 4.41 (1H, s), 4.21 (1H, m), 3.39-3.30 (1H, m), 3.21-3.14 (1H, m), 3.01-2.87 (2H, m), 2.51 (3H, s), 1.29 and 1.24 (3H, s). m/z (ES^+, 70V) 494.0 (MH^+).

EXAMPLE 25

Ethyl (2*S*)-2-[(4*R,S*)-4-benzyl-4-methyl-3-oxo-1-cyclobutenyl]amino-3-4-[(3,5-dichloroisonicotinoyl)amino]phenylpropanoate

Prepared from Intermediate 8 (185mg, 0.98mmol) and the free base of Intermediate 27 (300mg, 0.79mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (387mg, 0.70mmol, 89%) as an approx. 1:1 mixture of diastereomers. δH ($CDCl_3$, 300K) 9.36 and 9.31 (1H, s), 8.36 and 8.35 (2H, s), 7.54 and 7.45 (1H, d, J 8.4Hz), 7.19-7.02 (8H, m), 6.09-6.03 (1H, m), 4.31 and 4.20 (1H, s), 4.22-4.01 (3H, m), 3.07-2.92 (2H, m), 2.76-2.63 (2H, m), 1.35-1.15 (2H, m), 1.09 and 1.08 (3H, s). m/z (ES^+, 70V) 551.9 and 553.9 (MH^+).

EXAMPLE 26

(2*S*)-2-[(4*R,S*)-4-Benzyl-4-methyl-3-oxo-1-cyclobutenyl]amino-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 25 (320mg, 0.58mmol) was hydrolysed in a similar manner to the method of Example 12 to give the title compound as a fine white solid (277mg, 0.53mmol, 91%) as an approx. 1:1 mixture of diastereomers. δH (DMSO d^6, 360K) 13.05 (1H, br s), 8.83 and 8.82 (2H, s), 8.67 and 8.62 (1H, d, J 8.9Hz), 7.71 and 7.61 (2H, d, J 8.7Hz), 7.37-6.89 (9H, m), 4.32 and 4.23 (1H, s), 4.09-4.00 (1H, m), 3.20-2.64 (4H, m), 1.24-1.07 (3H, m). m/z (ES^+, 70V) 523.9 and 525.9 (MH^+).

EXAMPLE 27

Ethyl (2*S*)-2-[(3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Prepared from 1-keto-3-hydroxyspiro[3,5]-non-2-ene (400mg, 2.6mmol) [prepared according to the method of Wasserman, H.H. *et al*, J. Org. Chem., 38, 1451-1455 (1973)] and the free amine of Intermediate 27 (400mg, 1.04mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (512mg, 0.99mmol, 95%). δH ($CDCl_3$, 300K) 10.86 (1H, s), 8.78 (2H, s), 8.34 (1H, d, J 8.5Hz), 7.56 (2H, d, J 8.5Hz), 7.25 (2H, d, J 8.5Hz), 4.36 (1H, s), 4.20-4.11 (3H, m), 3.13 (1H, dd, J 13.8, 5.3Hz), 3.00 (1H, dd, J 9.2, 13.8Hz), 1.67-1.19 (10H, m), 1.17 (3H, t, J 4.1Hz). m/z (ES^+, 70V) 516.0 and 518.0 (MH^+).

EXAMPLE 28

(2*S*)-2-[(3-Oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 27 (700mg, 1.36mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (627mg, 1.28mmol, 95%). δ H (DMSO d^6, 360K) 10.54 (1H, s), 8.73 (2H, s), 7.81 (1H, d, J 8.4Hz), 7.56 (2H, d, J 8.5Hz), 7.27 (2H, d, J 8.5Hz), 4.39 (1H, s), 4.12-4.05 (1H, m), 3.19 (1H, dd, J 13.9, 5.1Hz), 3.00 (1H, dd, J 13.9, 8.8Hz), 1.94-1.24 (10H, m). m/z (ES^+, 70V) 488.0 and 490.0 (MH^+).

EXAMPLE 29

Ethyl (2*S*)-2-[(3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3-

methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

Prepared from 1-keto-3-hydroxyspiro[3,5]-non-2-ene (400mg, 2.6mmol) and Intermediate 20 (400mg, 1.14mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (497mg, 1.02mmol, 89%). δ H ($CDCl_3$, 300K) 9.62 (1H, s), 8.72 (1H, d, J 5.7Hz), 7.99 (1H, d, J 8.6Hz), 7.73 (1H, dd, J 5.7, 0.9Hz), 7.37-7.34 (3H, m), 7.28-7.24 (2H, m), 4.42 (1H, s), 4.26-4.18 (3H, m), 3.25 (1H, dd, J 14.0, 5.6Hz), 3.12 (1H, dd, J 14.0, 9.1Hz), 2.42 (3H, s), 1.72-1.55 (10H, m), 1.25 (3H, t, J 7.1Hz). m/z (ES^+, 70V) 486.1 (MH^+).

EXAMPLE 30

(2S)-2-[(3-Oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3-methyl[2,7] naphthyridin-1-yl)oxy]phenyl}propanoic acid

The compound of Example 29 (300mg, 0.62mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (237mg, 0.52mmol, 84%). δH (DMSO d^6, 360K) 9.62 (1H, s), 8.72 (1H, d, J 5.7Hz), 7.82 (1H, d, J 6.3Hz), 7.73 (1H, d, J 5.5Hz), 7.35 (2H, d, J 8.7Hz), 7.25 (2H, d, J 8.7Hz), 4.39 (1H, s), 4.12 (1H, dd, J 8.7, 13.2Hz), 3.34-3.12 (2H, m), 2.42 (3H, s), 1.72-1.53 (10H, m). m/z (ES^+, 70V) 458.0 (MH^+).

EXAMPLE 31

Ethyl (2S)-2-[(2-bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

A solution containing the compound of Example 27 (500mg, 0.97mmol) and triethylamine (2eq, 270 μl) in THF (10ml) at 0° was treated dropwise with a solution of bromine (1.1eq, 170mg) in THF (5ml). After 20mins the reaction was allowed to warm to room temperature prior to dilution with EtOAc (100ml). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (20ml) and brine (20ml), dried ($MgSO_4$) filtered and concentrated *in vacuo*. The residual foam was chromatographed (SiO_2; EtOAc) to give the title compound as a white powder (511mg, 0.86mmol, 95%). δH ($CDCl_3$, 300K) 8.48 (2H, s), 8 .05 (1H, s br), 7.52 (2H, d J 8.4Hz), 7.04 (2H, d J 8.5Hz), 5.81 (1H, d br, J 8.3Hz), 4.98-4.91 (1H, m), 4.21 (2H, q, J 7.1Hz), 3.21 (2H, d J 5.3Hz), 1.70-1.66 (4H, m), 1.53-1.44

(4H, m), 1.28 (3H, t J 7.1Hz), 1.20-1.16 (2H, m). m/z (ES+, 70V) 597.9 and 595.0 (MH^+).

EXAMPLE 32

(2S)-2-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 31 (511mg, 0.86mmol) was hydrolysed in a similar manner to the method of Example 2 (1.3eq, 50mg), to give the title compound as a white powder (421mg, 0.74mmol, 87%). δH (DMSO d^6, 390K) 10.34 (1H, s), 8.67 (2H, s), 7.53 (2H, s br), 7.26 (2H, d J 8.26Hz), 4.67 (1H, m), 3.26-3.22 (1H, m), 3.13-3.08 (1H, m), 1.67-1.21 (10H, m). δC (DMSO-d^6, 300K) 23.86, 25.30, 30.75, 37.79, 57.98, 61.94, 67.02, 119.73, 128.47, 130.38, 133.46, 136.86, 142.85, 148.10, 160.11, 171.80, 173.96, 186.93. m/z (ES+, 70V) 569.9 and 567.9 (MH^+).

EXAMPLE 33

Ethyl (2S)-2-[(2-bromo-4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Bromine (1.1eq, 0.32ml) was added dropwise to a stirred solution of the compound of Example 5 (2.7g, 5.67mmol) in THF (25ml) at room temperature. After 25min the reaction was diluted with EtOAc (100ml) and the crude reaction mixture washed with saturated aqueous $NaHCO_3$ (20ml) and brine (20ml), dried ($MgSO_4$) filtered and concentrated *in vacuo*. The residual foam was chromatographed (SiO_2; EtOAc) affording the title compound as a pale yellow powder (2.51g, 4.53mmol, 76%). δH ($CDCl_3$, 300K) 8.46 (2H, s), 8.17 (1H, s br), 7.51 (2H, d J 8.4Hz), 7.04 (2H, d J 8.4Hz), 6.05 (1H, d br, J 8.4Hz), 4.98-4.92 (1H, m), 4.22 (2H, q, J 7.1Hz), 3.21 (2H, d J 5.4Hz), 1.28 (3H, t J 7.1Hz), 1.14 (3H, s), 1.13 (3H, s). m/z (ES+, 70V) 555.8 and 557.9 (MH^+).

EXAMPLE 34

(2S)-2-[(2-Bromo-4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 33 (198mg, 0.36mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a white powder (142mg, 0.27mmol, 75%). δH (DMSO-d^6, 390K) 10.46 (1H,

s), 8.74 (2H, s), 7.63 (2H, d J 5.74Hz), 7.35 (2H, d J 8.26Hz), 4.80 (1H, s br), 3.32 (1H, dd J 5.14, 14.2Hz), 3.14 (1H, dd J 8.9Hz 14.2Hz), 1.18 (3H, s), 1.15 (3H, s). m/z (ES$^+$, 70V) 527.9 and 529.8 (MH$^+$).

EXAMPLE 35

Ethyl (2S)-2-[(3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(2,7)naphthyridin-1-yloxy]phenyl}propanoate

A solution of the ethyl ester of Intermediate 13 (565mg, 1.68mmol) and 1-keto-3-hydroxyspiro[3,5]-non-2-ene (280mg, 1.84mmol) in DCM (20ml) was stirred at roon temperature for 24h. Concentration *in vacuo* and chromatography (SiO_2; EtOAc) to give the title compound as a pale yellow powder (730mg, 1.55mmol, 92%). δH ($CDCl_3$, 300K) 9.82 (1H, s), 8.82 (1H, d J 5.7Hz), 8.14 (1H, d J 5.9Hz), 7.64 (1H, d J 5.8Hz), 7.25-7.17 (6H, m), 5.77 (1H, d J 7.6Hz), 4.60 (1H, s), 4.25 (2H, q J 7.1Hz), 3.30 (1H, dd J 5.5Hz 13.9Hz), 3.18 (1H, dd J 5.5Hz 13.9Hz), 1.84-1.53 (10H, m), 1.35 (3H, t J 7.1Hz). m/z (ES$^+$, 70V) 472.1 (MH$^+$).

EXAMPLE 36

Ethyl (2S)-2-[(2-bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-{(2,7)naphthyridin-1-yloxy]phenyl}propanoate

A stirred solution of the compound of Example 35 (300mg, 0.637mmol) and triethylamine (1.2eq, 100 μl) at 0° was treated dropwise with a solution of bromine in DCM (2%wv/v, 2.1ml, 1.2eq). After 12h the reaction was diluted with DCM (50ml) and washed successively with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) filtered and concentrated *in vacuo*. The residual foam was triturated with diisopropylether and the resulting solid collected and dried *in vacuo* to give the title compound as a pale yellow powder (325mg, 0.59mmol, 95%). δH ($CDCl_3$, 300K) 9.83 (1H, s), 8.78 (1H, d J 5.8Hz), 8.16 (1H, d J 5.8Hz), 7.69 (1H, d, J 5.7Hz), 7.32 (1H, d, J 5.8Hz), 7.27 (4H, s), 5.87 (1H, d, J 8.4Hz), 5.10-5.03 (1H, m), 4.30 (2H, q, J 7.1Hz), 3.38-3.32 (2H, m), 1.85-1.69 (4H, m), 1.67-1.50 (6H, m), 1.36 (3H, t, J 7.1Hz). m/z (ES$^+$, 70V) 552.0 (MH$^+$).

EXAMPLE 37

(2S)-2-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(2,7)naphthyridin-1-yloxy]phenyl}propanoic acid

The compound of Example 36 (220mg, 0.40mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white powder (125mg, 0.24mmol, 60%). δH (DMSO-d^6, 300K) 9.27 (1H, s), 8.88 (1H, d J 9.4Hz), 8.83 (1H, d J 5.4Hz), 8.12 (1H, d J 5.8Hz), 7.90 (1H, d J 5.7Hz), 7.55 (1H, d J 5.8Hz), 7.38 (2H, d J 8.4Hz), 7.27 (2H, d J 8.4Hz), 4.83-4.79 (1H, m), 3.08-3.03 (2H, m), 1.80-1.37 (8H, m), 1.19-1.12 (2H, m). m/z (ES+, 70V) 523.9 (MH^+).

EXAMPLE 38

Ethyl (2S)-2-[(3-oxo-7-oxaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Prepared from 7-oxaspiro[3.5]nonane-1,3-dione (1.2g, 7.8mmol) and the free amine of Intermediate 27 (2.67g, 7.0mmol) in a similar manner to the method of Example 11, to give the title compound (3.31g, 6.38mmol, 91%). δH ($CDCl_3$, 300K) 8.61 (1H, s), 8.33 (2H, s), 7.41 (2H, d J 5Hz), 6.94 (2H, d J 8.5Hz), 6.30 (1H, s br), 4.35 (1H, s), 4.11 (2H, q J 7.1Hz) and (1H, m obscured), 5.72 (4H, m), 3.07 (1H, dd J 14.0, 5.0 Hz), 2.94 (1H, dd J 14.0, 6.6Hz), 1.75-1.66 (2H, m), 155-1.48 (2H, m), 1.17 (3H, t J 7.1Hz). m/z (ES+, 70V) 517.9 (MH^+).

EXAMPLE 39

Ethyl (2S)-2-[(2-bromo-3-oxo-7-oxaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

A solution of the compound of Example 38 (1.64g, 3.17mmol) and triethylamine (0.69g, 970 µl, 6.8mmol) in THF (15ml) at 0° was treated dropwise with a solution of bromine (560mg, 3.1mmol) in THF (2ml). After 1h the resulting precipitate was removed by filtration, washed several times with cold EtOAc and dried to give the title compound as a white powder (1.53g, 2.56mmol, 81%). δH (DMSO d^6, 300K) 10.90 (1H, s), 9.07 (1H, d J 9.0Hz), 8.81 (2H, s), 7.60 (2H, d J 8.4Hz), 7.28 (2H, d J 8.4Hz), 4.85-4.80 (1H, m), 4.21 (2H, q J 7.1Hz), 3.81-3.76 (2H, m), 3.63-3.58 (2H, m), 3.23 (1H, dd J 13.8, 4.8Hz), 3.05 (1H, dd J 13.8, 9.4Hz), 2.07-1.94 (2H, m), 1.52-1.49 (1H, m), 1.34-1.31 (1H, m), 1.24 (3H, t J 7.1Hz). m/z (ES+, 70V) 597.9 and 599.9 (MH^+).

EXAMPLE 40

(2*S*)-2-[(2-Bromo-3-oxo-7-oxaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 39 (575mg, 0.96mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white powder (283mg, 0.50mmol, 52%). δH (DMSO d^6, 390K) 10.88 (1H, s), 8.98 (1H, d J 9.2Hz), 8.81 (2H, s), 7.59 (2H, d J 8.5Hz), 7.27 (2H, d J 8.5Hz), 4.78-4.72 (1H, m), 3.82-3.75 (2H, m), 3.64-3.54 (2H, m), 3.24 (1H, dd J 13.9, 4.5Hz), 3.01 (1H, dd J 13.8, 9.5Hz), 2.08-1.93 (2H, m), 1.52-1.48 (1H, m), 1.30-1.26 (1H, m). m/z (ES^+, 70V) 569.9 and 571.9 (MH^+).

EXAMPLE 41

Methyl (2*S*)-2-{(3-oxospiro[3.5]non-1-en-1-yl)amino}-3-(2,6-dimethoxy[1,1'-biphenyl]-4-yl)propanoate

To a solution of methyl (2*S*)-2-amino-3-(2,6-dimethoxy[1,1'-biphenyl]-4-yl)propanoate (0.80g, 2.5mmol) in DCM (10ml) at room temperature was added 1-keto-3-hydroxyspiro[3,5]-non-2-ene (0.38g, 2.5mmol) and the mixture stirred for 48h. Volatiles were removed *in vacuo* and the residue purified by column chromatography (SiO_2; EtOAc) to give the title compound as a white solid (1.05g, 92%). δH ($CDCl_3$): 7.32-7.26 (3H, m), 7.12 (2H, d, J 8.2Hz), 6.92 (2H, d, J 8.3Hz), 5.90 (1H, br d, J 8.2Hz), 4.60 (1H, s), 4.33 (1H, br), 3.86 (3H, s), 3.73 (6H, s), 3.30 (1H, dd, J 13.9, 5.3Hz), 3.13 (1H, dd, J 13.9, 6.3Hz), 1.82 -1.33 (10H, m). m/z (ES^+, 70V) 450.1 (MH^+).

EXAMPLE 42

(2*S*)-2-{(3-Oxospiro[3.5]non-1-en-1-yl)amino}-3-(2,6-dimethoxy[1,1'-biphenyl]-4-yl)propanoic acid

The compound of Example 41 (0.40g, 0.9mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white solid (0.19g, 45%). δH (DMSO d^6) 8.25 (1H, d, J 8.6Hz), 7.29-7.19 (3H, m), 7.07 (2H, d, J 7.9Hz), 6.70 (2H, d, J 8.4Hz), 4.32 (1H, s), 4.11 (1H, br), 3.61 (6H, s), 3.18 (1H, dd, J 13.7, 4.7Hz), 2.93 (1H, dd, J 13.7 9.9Hz), 1.67-1.16 (10H, m). m/z (ES^+, 70V) 436.1 (MH^+).

EXAMPLE 43

Methyl (2S)-2-{(2-bromo-3-oxospiro[3.5]non-1-en-1-yl)amino}-3-(2,6-dimethoxy[1,1'-biphenyl]-4-yl)propanoate

To a cooled solution (0-5°C) of the compound of Example 41 (0.42g, 0.93mmol) and triethylamine (0.14ml, 1.03mmol) in THF (10ml) was added a solution of bromine (0.16g, 1.0mmol) in DCM (1ml). The mixture was stirred at this temperature for 1h prior to partitioning between EtOAc (100ml) and sodium hydrosulfite (100ml, 5% aq.). The organics were separated, washed with water (50ml), brine (50ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as pale yellow foam. Column chromatography (SiO_2, 1:1 EtOAc: hexanes) gave the title compound as a white foam (0.45g, 92%). δH ($CDCl_3$) 7.32-7.26 (3H, m), 7.13 (2H, d, J 8.1Hz), 6.66 (2H, d, J 8.4Hz), 5.80 (1H, br d, J 8.6Hz), 5.15-5.08 (1H, m), 3.87 (3H, s), 3.73 (6H, s), 3.35 (1H, d, J 10.0Hz), 3.31 (1H, d, J 4.9Hz), 1.80-1.33 (10H, m). m/z (ES^+, 70V) 529.0 and 530.0 (MH^+).

EXAMPLE 44

(2S)-2-{(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino}-3-(2,6-dimethoxy[1,1'-biphenyl]-4-yl)propanoic acid

The compound of Example 43 (0.36g, 0.7mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a white solid (0.23g, 58%). δH (DMSO d^6) 8.83 (1H, d, J 9.4Hz), 7.28 (1H, d, J 8.4Hz), 7.24-7.20 (2H, m), 7.10 (2H, d, J 8.1Hz), 6.70 (2H, d, J 8.4Hz), 4.83-4.77 (1H, br), 3.61 (6H, s), 3.25 (1H, dd, J 13.8, 9.8Hz), 2.95 (1H, dd, J 13.8, 10.3Hz), 1.78-1.35 (10H, m). m/z (ES^+, 70V) 516.0 and 517.0 (MH^+).

EXAMPLE 45

Ethyl (2S)-2-[(3-oxospiro[3.6]dec-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Prepared from Intermediate 31 (400mg, 2.4mmol) and the free amine of Intermediate 27 (920mg, 2.4mmol) in a similar manner to the method of Example 11, to give the title compound (1.1g, 20.7mmol, 86%). δH ($CDCl_3$, 300K) 8.57 (2H, s), 8.28 (1H, s), 7.61 (2H, d J 8.5Hz), 7.14 (2H, d J 8.5Hz), 5.76 (1H, d J 7.5Hz), 4.33-4.23 (3H, m), 3.25 (1H, dd J 5.3, 14.0Hz), 3.12 (1H, dd J 5.7, 13.9 Hz), 1.95-1.89 (2H, m), 1.79-1.70 (4H, m), 1.71-1.50 (6H, m), 1.36 (3H, t J 7.1Hz). m/z (ES^+, 70V) 530.0 (MH^+).

EXAMPLE 46

(2S)-2-[(3-Oxospiro[3.6]dec-1-en-1-yl)amino]3-{4-[(3,5-dichloroiso-nicotinoyl)amino] phenyl}propanoic acid.

The compound of Example 45 (257mg, 0.57mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white powder (257mg, 0.51mmol, 89%). δH (DMSO d^6, 390K) 10.83 (1H, s), 8.84 (2H, s), 7.39 (2H, d J 8.5Hz), 7.29 (2H, d J 8.5Hz), 4.30 (1H, s), 4.12-3.98 (1H, m), 3.15 (1H, dd J 13.9, 5.2Hz), 2.97 (1H, dd J 13.8, 9.5Hz), 1.85-1.78 (1H, m), 1.77-1.38 (11H, m). m/z (ES^+, 70V) 502.0 (MH^+).

EXAMPLE 47

Ethyl (2S)-2-[(2-bromo-3-oxospiro[3.6]dec-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate.

A solution of the compound of Example 45 (988mg, 1.87mmol) and triethylamine (520 µl, 3.7mmol) in THF (20ml) at 0°C was treated dropwise with a solution of bromine (330mg, 2.1mmol) in THF (2ml). After 1h the crude reaction mixture was diluted with EtOAc (50ml), saturated aqueous $NaHCO_3$ (15ml) and saturated aqueous sodium chloride (15ml) and the crude product extracted with EtOAc (3 x 20ml). The combined extracts were dried ($MgSO_4$), concentrated *in vacuo* and the crude residue chromatographed (SiO_2, 1:1 ethyl acetate:hexanes) to give the title compound as a white powder (965mg, 1.58mmol, 85%). δH ($CDCl_3$, 300K) 8.61 (2H, s), 8.45 (1H, d, J 3.1Hz), 7.63 (2H, d, J 8.2Hz), 7.15 (2H, d, J 8.2Hz), 5.91 (1H, d, J 8.1Hz), 5.05-5.00 (1H, m), 4.30 (2H, q, J 7.1Hz), 3.30 (2H, d, J 5.4Hz), 1.98-1.90 (2H, m), 1.89-1.60 (10H, m), 1.22 (3H, t, J 7.1Hz). m/z (ES^+, 70V) 609.9 and 611.9 (MH^+).

EXAMPLE 48

(2S)-2-[(2-Bromo-3-oxospiro[3.6]dec-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 47 (560mg, 0.92mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white powder (412mg, 0.71mmol, 77%). δH (DMSO d^6, 380 K) 10.40 (1H, s), 8.67 (2H, s), 7.55 (2H, d, J 8.5Hz), 7.26 (2H, d , J 8.5Hz), 4.52

(1H, br s), 3.22 (1H, dd, J 14.1, 5.3Hz), 3.11 (1H, dd , J 13.9, 8. 0H z), 1.82-1.29 (12H, m). m/z (ES^+, 70V) 589.1 and 583.9 (MH^+).

EXAMPLE 49

Ethyl (2S) 2-{[4,4-dimethyl-2-(phenylselenenyl)-3-oxo-1-cyclobutenyl] amino}3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

A stirred solution of the compound of Example 5 (630mg, 1.41mmol) in THF (15ml) at room temperature was treated dropwise with a solution of phenylselenenyl chloride (283mg, 1.48mmol). After 10min the crude reaction mixture was diluted with EtOAc (30ml) saturated aqueous $NaHCO_3$ solution (50ml) and brine (50ml). The mixture was extracted with EtOAc (3 x 50ml), the combined extracts dried ($MgSO_4$) and concentrated *in vacuo*. The residual slurry was chromatographed (SiO_2, EtOAc) to give the title compound as a white powder (812mg, 1.29mmol, 91%). δH ($CDCl_3$, 300K) 8.58 (2H, s), 7.75 (1H, s), 7.53 (2H, d , J 8.3Hz), 7.35-7.11 (5H, m), 7.04 (2H, d, J 8.3Hz), 6.11 (1H, d, J 8.5Hz), 5.28-5.25 (1H, m), 4.20 (2H, q, J 7.1Hz), 3.17 (2H, m), 1.31 (6H, s), 1.28 (3H, t , J 7.1Hz). m/z (ES^+, 70V) 631.9 (MH^+).

EXAMPLE 50

(2S)- 2-{[4,4-dimethyl-2-(phenylselenenyl)-3-oxo-1-cyclobutenyl] amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 49 (600mg, 0.95mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white powder (503mg, 0.83mmol, 87%). δH (DMSO d^6, 300K) 10.86 (1H, s), 9.11 (1H, d, J 8.9Hz), 8.81 (2H, s), 7.50 (2H, d, J 8.2Hz), 7.21 (2H, d, J 8.2Hz), 4.96-4.92 (1H, br s), 3.13 (1H, dd, J 13.8, 4.5Hz), 2.94 (1H, dd, J 13.6, 8.7Hz), 1.22 (3H, s), 1.14 (3H, s). m/z (ES^+, 70V) 603.9 (MH^+).

EXAMPLE 51

Ethyl (2S)-2-[(3-oxo-7-acetyl-7-azaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate.

Prepared from Intermediate 33 (150mg, 0.77mmol), and the free amine of Intermediate 27 (150mg, 0.39mmol) in a similar manner to the method of Example 11, to give the title compound (143mg, 0.26mmol, 67%). δH

(DMSO d^6, 300K) 10.89 (1H, s), 8.89 (2H, s), 8.55-8.48 (1H, m), 7.58 (2H, d, J 7.9Hz), 7.25 (2H, d, J 7.9Hz), 4.47 (1H, s), 4.29-4.23 (1H, m), 4.16 (2H, q, J 7.1Hz), 3.76-3.72 (1H, m), 3.15 (1H, dd, J 13.8, 5.2Hz), 3.01-2.89 (2H, m), 2.00 (3H, s), 1.90-1.37 (6H, m), 1.21 (3H q J 7.1Hz). m/z (ES$^+$, 70V) 559.0 (MH^+).

EXAMPLE 52

(2S)-2-[(3-Oxo-7-acetyl-7-azaspiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 51 (200mg, 0.35mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white powder (91mg, 0.16mmol, 46%). δH (CD_3OD, 300K) 8.90 (2H, s), 7.60 (2H, d, J 8.2Hz), 7.30 (2H, J 8.2Hz), 4.49 (1H, s), 4.33-4.27 (2H, m), 3.85-3.77 (1H, m), 3.57-3.45 (1H, m), 3.37-3.31 (1H, m), 3.20-3.11 (1H, m), 3.05-2.99 (1H, m), 2.11 (3H, s), 1.97-1.52 (4H, m). m/z (ES$^+$, 70V) 531.0 (MH^+).

EXAMPLE 53

Ethyl (2S)-2-[(7-methoxy-3- oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Prepared from Intermediate 35 (500mg, 2.77mmol) and the free amine of Intermediate 27 (980mg, 2.6mmol) in a similar manner to the method of Example 11, to give the title compound as an inseparable 1:1 mixture of isomers (1.23g, 2.25mmol, 87%). δH ($CDCl_3$, 300K, 2 isomers) 9.12/8.99 (1H, s), 8.51/8.50 (2H, s), 7.59/7.56 (2H, d, J 8.5Hz), 7.08 (2H, d, J 8.5Hz), 6.21/5.98 (1H, d, J 7.9Hz/7.6Hz), 4.46/4.43 (1H, s), 4.29/4.10 (3H, m), 3.13-3.08 (1H, m), 3.39 (1H, m), 3.30/3.29 (3H, s), 3.23-3.18 (1H, m), 3.13-3.08 (1H, m), 1.97-1.58 (8H, m), 1.35-1.34 (3H, t, J 7.1Hz). m/z (ES$^+$, 70V) 546.0 (MH^+).

EXAMPLE 54

(2S)-2-[(7-Methoxy-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 53 (950mg, 1.7mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white powder, as an approx. 1:1 mixture of isomers (812mg, 1.57mmol,

92%). δH (DMSO d^6, 300K) 10.57 (1H, s), 8.73 (2H, s), 7.93 (1H, br s), 7.56 (2H, d, J 8.2Hz), 7.29-7.21 (2H, m), 4.37 (1H, s), 4.08-4.04 (1H, m), 3.34 (1H, m), 3.25 (3H, s), 3.21-3.02 (2H, m), 1.92-1.34 (8H, m). m/z (ES^+, 70V) 518.0 (MH^+).

EXAMPLE 55

Ethyl (2S)-2-[(2-bromo-7-methoxy-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Was prepared according to the method of Example 47 from the compound of Example 53 (1.0g, 1.83mmol) and bromine (322mg, 2.0mmol) to give the title compound as a powder (778mg, 1.24mmol, 70%). [Separation of isomers at this stage was achieved chromatographically (SiO_2; 1:1 EtOAc:hexanes to 100% EtOAc)]. δH ($CDCl_3$, 300K, fast eluting isomer) 10.65 (1H, s), 10.74 (1H, d, J 9.2Hz), 8.58 (2H, s), 7.36 (2H, d, J 8.6Hz), 7.06 (2H, d, J 8.6Hz) 4.54-4.48 (1H, m), 3.18 (1H, m), 3.03-2.98 (1H, m), 3.00 (3H, s), 2.78 (1H, dd, J 13.9, 10.0Hz), 1.18-1.65 (2H, m), 1.61-1.44 (4H, m), 1.18-1.15 (1H, m), 0.92 (1H, m). m/z (ES^+, 70V) 625.9 (MH^+).

EXAMPLE 56

(2S)-2-[(2-Bromo-7-methoxy-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 55 (650mg, 1.04mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white powder (512mg, 0.86mmol, 83%). δH (DMSO d^6, 300K) 10.86 (1H, s), 9.11 (1H, d , J 8.9Hz), 8.81 (2H, s), 7.50 (2H, d, J 8.2Hz), 7.21 (2H, d, J 8.2Hz), 4.96-4.92 (1H, br s), 3.13 (1H, dd, J 13.8, 4.5Hz), 2.94 (1H, dd, J 13.6, 8.7 Hz), 1.22 (3H, s), 1.14 (3H, s). m/z (ES^+, 70V) 597.9 (MH^+).

EXAMPLE 57

Ethyl (2S)-2-[(2-bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

To the compound of Example 29 (0.54g, 1.1mmol) in THF (10ml) at room temperature was added triethylamine (0.2ml, 1.4mmol) and a solution of bromine (224mg, 1.4mmol) in DCM (1ml). The mixture was stirred overnight and then partitioned between EtOAc (50ml) and water (50ml).

The organics were separated, washed with sodium hydrosulfite (2 x 50ml, 5% aq.), water (50ml), brine (50ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was subjected to column chromatography (SiO_2; EtOAc) to give the title compound as a white solid (0.46g, 73%). δH ($CDCl_3$) 9.75 (1H, s), 8.69 (2H, d, J 5.9Hz), 7.64 (2H, d, J 6.0Hz), 7.25 (2H, d, J 8.2Hz), 7.20 (2H, d, J 8.2Hz), 5. 89 (1H, d, J 8.3Hz), 5.06 (1H, dt, J 5.4, 8.2Hz), 4.30 (2H, q, J 7.1Hz), 3.35 (2H, m), 2.50 (3H,s), 1.84-1.33 (10H, m). m/z (ES^+, 70V) 566.1 and 567.1 (MH^+).

EXAMPLE 58

(2S)-2-{(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino}-3-{4-[(3-methyl[2.7]naphthyridin-1-yl)oxy]phenyl}propanoic acid

The compound of Example 57 (0.32g, 0.6mmol) was hydrolysed in a similar manner to the method of Example 2, to give the title compound as a white solid (0.20g, 66%). δH (DMSO d^6) 9.61 (1H, s), 8.88 (1H, d, J 9.5Hz), 8.72 (1H, d, J 5.7Hz), 7.74 (1H, d , J 5.8Hz), 7.35 (3H, c), 7.24 (2H, d , J 8.6Hz), 4.77 (1H, m), 3.18 (1H, dd, J 13.7, 4.70Hz), 3.01 (1H, dd, J 13.7, 10.4H z), 2.49 (3H, s), 1.78-1.12 (10H, m). m/z (ES^+, 70V) 537.1 and 538.1 (MH^+).

EXAMPLE 59

Ethyl (2S)-2-{[2-(phenylsulfanyl)-4,4-dimethyl-3-oxo-1-cyclobutenyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl} propanoate

A solution of the compound of Example 5 (340mg, 0.76mmol) in THF (25ml), at room temperature, was treated dropwise with a solution containing phenyl sulphenyl chloride (122mg, 0.84mmol) in THF (2ml). After 10min the reaction mixture was poured into a mixture of EtOAc (150ml) and saturated aqueous $NaHCO_3$ solution (50ml). The organic layer was extracted and washed with brine (25ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (SiO_2; 100% EtOAc) gave the title compound as a white powder (346mg, 0.59mmol, 78%). δH ($CDCl_3$) 8.45 (2H, s), 8.05 (1H,, s), 7.43 (1H, d, J 8.4Hz), 7.15 (2H, d, J 8.4Hz), 7.11-7.04 (5H, m), 6.25 (1H, d, J 8.5Hz), 5.10-5.05 (1H, m), 4.09 (2H, q, J 7.1Hz), 3.11-3.06 (2H, m), 1.18 (3H, s), 1.15 (3H, s), 1.13 (3H, t, 7.1Hz). m/z (ES^+, 70V) 584.0 (MH^+).

EXAMPLE 60

(2S)-2-{[2-(Phenylsulfanyl)-4,4-dimethyl-3-oxo-1-cyclobutenyl]-amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

Hydrolysis of the ethyl ester (340mg, 0.58mmol) with lithium hydroxide (60mg, 1.4mmol), according to the method of Example 2, gave the title compound (29 6 mg, 0.53mmol, 90%) as a white powder. δH (DMSO d^6, 390K) 10.30 (1H, br s), 8.68 (2H, s), 7.45 (2H, br s), 7.26-7.22 (2H, m), 7.15-7.08 (7H, m), 4.75-4.66 (1H, m), 3.17 (1H, dd, J 14.0, 5.3Hz), 3.04 (1H, dd , J 14.0, 7.7Hz), 1.19 (3H, s), 1.16 (3H, s). m/z (ES^+, 70V) 556.0, 557.9 (MH^+).

EXAMPLE 61

Ethyl (2S)-2-[(2-chloro-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

A solution of the compound of Example 27 (366mg, 0.71mmol) in THF (25ml), at room temperature, was treated portionwise with N-chloro succinimide (100mg, 0.75mmol). After 30min the reaction mixture was poured into a mixture of EtOAc (150ml) and saturated aqueous $NaHCO_3$ solution (50ml). The organic layer was extracted and washed with brine (25ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (SiO_2; 70% EtOAc:hexanes) gave the title compound as a white powder (312mg, 0.56mmol, 80%). δH ($CDCl_3$) 8.50 (2H, s), 7.73 (1H, s), 7.53 (1H, d, J 8.4Hz), 7.04 (2H, d, J 8.4Hz), 5.73 (1H, d, J 8.0Hz), 4.88-4.81 (1H, m), 4.21 (2H, q, J 7.1Hz), 3.21-3.16 (2H, m), 1.79-1.65 (4H, m), 1.51-1.36 (6H, m), 1.28 (3H, t, J 7.1Hz). m/z (ES^+,70V) 550.0 (MH^+).

EXAMPLE 62

(2S)-2-[(2-Chloro-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

Hydrolysis of the compound of Example 61 (300mg, 0.54mmol) with lithium hydroxide (60mg, 1.4mmol), according to the method of Example 2, gave the title compound. δH (DMSO d^6, 390K) 10.44 (1H, br s), 8.69 (2H, s), 8.05-7.85 (1H, s br), 7.54 (2H, d, J 7.8Hz), 7.25 (2H, d, J 7.8Hz),

dd, J 14.0, 5.3Hz), 3.04 (1H, dd, J 14.0, 5.1Hz), 1.80-1.21 (10H, m). m/z (ES^+, 70V) 521.9, 525.9 (MH^+).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with $F(ab)_2$ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 µl at 2 µg/ml in 0.1M $NaHCO_3$, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 µl containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100µl methanol for 10 minutes followed by another wash. 100µl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100µl 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β-lympho blastoid cell-line JY was used in place of Jurkat cells. The IC_{50} value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5μg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100μl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200μl containing 2.5x 10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$-dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200μl in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100μl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50μg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

αIIb/β_3 -dependent human platelet aggregation

Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10^8/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl

8.0; $MgCl_2.H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0; $NaHPO_4.2H_2O$ 0.065). Aggregation was monitored following addition of 2.5μM ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the preferred compounds of the invention such as the compounds of the Examples generally have IC_{50} values in the $\alpha_4\beta_1$ and assay of 1 μM and below and in the $\alpha_4\beta_7$ assay of 5μM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50μM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.